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Editorial

Healthy Lifestyle Can Reduce the Alzheimer's Disease

Mohsin Masud Jan
Editor

Alzheimer's is the most common cause of dementia. Alzheimer's is not a normal part of aging. Dementia is second leading cause of death and the leading cause of death among females. There are many ways you can become involved in Dementia Awareness Month to show your support. Don't face dementia alone. Alzheimer's Disease diagnoses are growing at an exponential rate, and treating it is one of the costliest efforts. Early detection not only improves quality of life, but also can massively reduce the costs associated with treating Alzheimer's Disease. It is only through a truly global effort that we can raise much needed awareness and challenge the stigma and misinformation that still surrounds dementia.

A general term for memory loss and other cognitive abilities serious enough to interfere with daily life. Alzheimer's disease accounts for 60-80 per cent of dementia cases.

The greatest known risk factor is increasing age, and the majority of people with Alzheimer's are 65 and older. Alzheimer's disease is considered to be younger-onset Alzheimer's if it affects a person under 65. Younger-onset can also be referred to as early-onset Alzheimer's. People with younger-onset Alzheimer's can be in the early, middle or late stage of the disease.

Alzheimer's is a progressive disease, where dementia symptoms gradually worsen over a number of years. In its early stages, memory loss is mild, but with late-stage Alzheimer's, individuals lose the ability to carry on a conversation and respond to their environment. On average, a person with Alzheimer's lives 4 to 8 years after diagnosis but can live as long as 20 years, depending on other factors.

Alzheimer's has no cure, but one treatment - Aducanumab (Aduhelm) — is the first therapy to demonstrate that removing amyloid, one of the hallmarks of Alzheimer's disease, from the brain is reasonably likely to reduce cognitive and functional decline in people living with early Alzheimer's. Other treatments can temporarily slow the worsening of dementia symptoms and improve quality of life for those with Alzheimer's and their caregivers. Today, there is a worldwide effort underway to find better ways to treat the disease, delay its onset and prevent it from developing.

A healthy lifestyle can make a difference in Alzheimer's prevention.

As the exact cause of Alzheimer's disease is still unknown, there's no certain way to prevent the condition. But a healthy lifestyle can help reduce your risk. The research concluded that by modifying all the risk factors we're able to change, our risk of dementia could be significantly reduced.

Cardiovascular disease has been linked with an increased risk of Alzheimer's disease and vascular dementia. You may be able to reduce your risk of developing these conditions – as well as other serious problems, such as strokes and heart attacks – by taking steps to improve your cardiovascular health. These include:

- reduce smoking.
- keeping alcohol to a minimum.
- eating a healthy, balanced diet, including at least 5 portions of fruit and vegetables every day.
- exercising for at least 150 minutes every week by doing moderate-intensity aerobic activity (such as cycling or fast walking), or as much as you're able to.
- making sure your blood pressure is checked and controlled through regular health tests.
- if you have diabetes, make sure you keep to the diet and take your medicine.

There's some evidence to suggest that rates of dementia are lower in people who remain mentally and socially active throughout their lives. It may be possible to reduce your risk of Alzheimer's disease and other types of dementia by:

- reading.
- learning foreign languages.
- playing musical instruments.
- volunteering in your local community.
- taking part in group sports, such as bowling.
- trying new activities or hobbies.
- maintaining an active social life.
- Interventions such as "brain training" computer games have been shown to improve cognition over a short period, but research has not yet demonstrated whether this can help prevent dementia.

The latest research suggests that other factors are also important, although this does not mean these factors are directly responsible for causing dementia.

These include:

- hearing loss.
- untreated depression (although this can also be a symptom of dementia).
- loneliness or social isolation.
- a sedentary lifestyle.

Early detection and healthy lifestyle can reduce the Alzheimer's disease.

Original Article

Are Vitamin D Levels Related to Serum Renin Levels in Hypertensive Patients?

Saima Mukhtar[1], Sara Naeem[1], Mah-E-Jabeen Sear[1], Iram Qamar[1], Shaista Hussain[2] and Humaira Hashmat[3]

ABSTRACT

Objective: To correlate vitamin D levels with serum renin levels in hypertensive male subjects.
Study Design: Analytical case control study
Place and Duration of Study: This study was conducted at the Lahore General Hospital, Lahore from January to June 2015.
Materials and Methods: The participants in this study were 75 male individuals were separated into stage I and stage II hypertension groups, with healthy attendants serving as controls. Subjects' blood pressure was recorded with a mercury sphygmomanometer, and blood samples were obtained for examination of vitamin D and renin levels.
Results: Subjects included had a mean age of 39.97 ± 8.24 years. Mean vitamin D levels (ng/mL) were 35.99 ± 8.08, 28.71 ± 10.85 and 28.12 ± 9.94 in controls, stage I hypertension and stage II hypertension groups respectively. The association between serum vitamin D and renin levels among the three groups was statistically significant with an 'r' value of -0.275 and p value of 0.017 as indicated in Table.1 and Fig.1.
Conclusion: Our findings in hypertensive patients showed an inverse relationship between blood pressure and vitamin D with an increase in levels of systolic BP, diastolic BP and plasma renin.
Key Words: Renin, Vitamin D, Hypertension

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INTRODUCTION

Stage I hypertension is defined as having a diastolic blood pressure of 90 to 99 mm Hg or a systolic blood pressure of 140 to 159 mm Hg. Stage II hypertension is defined as a systolic pressure of less than 160 mm Hg and/or a diastolic pressure of less than 100 mm Hg, according to James et al. (2014)[1]. The pathogenesis of hypertension is widely speculative. Essential hypertension is defined as having no underlying determinable cause and a tiny percentage of patients with an underlying renal or adrenal abnormality.

For the purposes of homeostasis, the RAAS is the prime director of body fluid volume, blood pressure, and salt equilibrium. Renin, an aspartyl protease, is the first component of RAAS,and it is produced by the juxtaglomerular (JG) cells of the renal glomerular afferent and partly efferent arterioles. By cleaving the N-terminal region of angiotensinogen, the enzyme renin works on the 2-globulin angiotensinogen generated in the liver and drives the synthesis of angiotensin I, a 10 amino acid peptide. The key step that controls the RAAS system is the production of physiologically inactive angiotensin I. Angiotensin converting enzyme (ACE), which is found in the epithelial lining of capillaries speeds up the hydrolytic removal of the C-terminal dipeptide from angiotensin I creating angiotensin II[2]. The physiologically active 8-amino-acid peptide hormone, Angiotensin II, affects tiny renal and systemic arteries to contract, raising total peripheral resistance and henceforth blood pressure. Angiotensin II transmits messages to the heart via brain sympathetic stimulation, resulting in increased cardiac output and, in combination with increased total peripheral resistance, higher blood pressure.

Mounting verification suggests vitamin D insufficiency plays a key task in the occurrence of cardiac risk elements and blood pressure-linked CVD. Four decades after being identified as a steroid hormone, vitamin D is still being studied today, and new chapters in its history are being revealed[3]. The biological reactions to 1, 25-(OH)2 D3 are mediated by the vitamin D receptor (VDR), which is found in the nucleus of a cell, according to Bikle[4]. VDR is a member of the retinoic acid, steroid, and thyroid hormone superfamily. Active vitamin D3 improves VDR's interaction with RXR

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(retinoic acid X receptor) in the cell nucleus. They interact to form a heterodimer called VDR/RXR. This complex binds to vitamin D response elements (VDREs), which are short DNA sequences, when 1, 25-dihydroxy vitamin D is present. Vitamin D's non-calcitropic actions are mediated by receptors of vitamin D and 1-hydroxylase, which are found in a wide range of human tissues. It influences insulin release, renin secretion from the RAAS, vascular genesis, programmed cell death, cell proliferation and differentiation, and immunological responses by controlling roughly 200 genes[5].

1, 25dihydroxy D3 acts as a negative endocrine controller of the RAAS as seen in adult male Wistar rats[6]. Vitamin D's significance in regulating renin gene expression and, eventually, blood pressure can be used to lower blood pressure. In the long run, these with fewer side effects may be able to take the position of angiotensin II receptor blockers and ACE inhibitors[7].

Vitamin D deficiency is thought to cause vascular smooth muscle and ventricular muscle hypertrophy as well as over activation of the renin-angiotensin-aldosterone pathway. The US government's recommendation to update the recommended vitamin D intake amounts for daily consumption and sun exposure is stressed[8].

With nearly one billion individuals suffering from insufficiency or deficiency, vitamin D deficiency has become a global epidemic[9, 10]. Vitamin D deficiency was once thought to be a rare occurrence in South Asia, but that has altered in recent years[11]. In a study conducted in Pakistan, deficient serum vitamin D levels was found in 163.4% patients, 14.9% patients showed insufficiency while only 21.8% had normal levels (>30 ng/ml)[12]. Vitamin D deficiency was shown to be prevalent in a sample of patients studied by Haque et al. in Lahore, with a frequency of 66% out of which 33% were hypertensive[13].

Studies further suggest that active vitamin D has a short-term BP lowering impact that is not seen with cholecalciferol administration, bolstering the theory of vitamin D's negative renin endocrine control. After a biweekly dosage of calcitriol it was found that blood pressure reduces from a starting value of 145/96 mm Hg to a concluding value of 128/85 mm Hg[14].

Vitamin D supplementation taken in conjunction with antihypertensive medicines for three months was likewise shown to dramatically lower systolic blood pressure. A putative participation of the RAAS system and calcium-regulating hormones has been proposed in this regard, according to several practical and logical explanations[15].

The enigma of the sunshine vitamin remains a source of debate in the Western realm, and the goal of our research was to learn more about the linkage between hypertension and vitamin D insufficiency in the Lahore populace. Once established, this would aid in the progress of our population by minimising the load of some threat variables such as hypertension and CVD through low-cost screening and vitamin D supplementation. This might have significant implications and consequences for patient management and health-care policy development.

MATERIALS AND METHODS

Seventy-five male individuals were recruited using non-probability convenience sampling from the outdoor department of Lahore General Hospital in Lahore, Pakistan, between September and December 2016. The cohort comprised of three groups of Controls: stage I, stage II hypertension, and stage III hypertension, each with 25 patients. Newly diagnosed hypertensive male patients aged 30-55 years were enrolled in the study and were divided into two groups: stage I and stage II patients, with healthy attendants serving as controls. Patients with secondary hypertension, poor vitamin D levels, or known renal, liver, thyroid, parathyroid, or cardiac disorders were not included in the study. Patients' medical histories, examinations, and laboratory tests were recorded on a questionnaire pro forma. An enzyme linked immunosorbent assay (ELISA) kit and an automated analyzer were used to perform the vitamin D test. Data was analyzed by SPSS 20.0. Vitamin D, SBP and DBP were described as mean and standard deviation (mean± SD).

Serum Renin was measured using a Human Renin ELISA kit and a conventional immunoassay (Creative Diagnostics, New York, USA). The wells of the microtiter plates are coated with an antibody that is specific for human renin. When pipetted into the wells, samples and standards bind to the coated antibody (Susan, 2010). This assay used an automated analyzer to quantify serum renin (STAT-FAX, model 303, USA).

Statistical Analysis: SPSS (Statistical Package for Social Sciences) version 20.0 was used to enter and analyse the data. The mean and standard deviation (mean SD) of vitamin D and renin levels were calculated. A one-way ANOVA (analysis of variance) was used to compare both variables between the three groups.

By comparing all feasible pairings of means, the post hoc Tukey test was used to determine whether means were substantially different from one another. To determine the relationship between dependent and independent variables, Pearson's co-efficient of correlation 'r' was used. An 'r' coefficient approaching 1 indicated a strong linear relationship between the two measured variables, whereas an 'r' value of 0 indicated no correlation between the two variables. A perfect positive relationship was represented by +1, whereas a perfect negative relationship was represented by -1. Statistical significance was defined as a p-value of less than 0.05.

RESULTS

The current study included 75 male volunteers aged 30-55 years old. They were separated into three groups, each with 25 participants.

Analyzing and comparing the mean SD renin (ng/mL) values in controls (3.51±3.57), stage I (4.81±3.98), and stage II hypertension groups (8.6 ±6.98) revealed that the difference between the control and stage I hypertension groups was non-significant (p=0.64), as shown in Table.1. When the control group was related to the stage II hypertension group, both were different statistically (p=0.002) (Table.1), and the variance in mean SD renin (ng/mL) between the stage I and stage II hypertension groups was significant statistically (p=0.02) (Table.1).

The Pearson's coefficient of correlation, or "r," was calculated to examine the link between the dependent variables (renin, aldosterone, systolic blood pressure, and diastolic blood pressure) and the independent factors (vitamin D) in the control, stage I, and stage II hypertension groups.

Table.1 and Fig.1 show that there was a statistically significant relationship between serum vitamin D and renin levels in the three groups, with an 'r' value of -0.275 and a p value of 0.017.

Table No.1: Comparison of vitamin D, Serum renin, Systolic and Diastolic BP in Control, Stage I Hypertension and Stage II Hypertension Groups

	Control (n=25)	Stage I Hypertension (n=25)	Mean difference	p-value
Vitamin D (ng/mL)	35.99±8.082	28.71±10.85	7.29	0.026*
Serum Renin (ng/mL)	3.51±3.57	4.81±3.98	-1.29	0.642†
Systolic BP (mm Hg)	110.72±5.59	131.20±8.83	-20.48	0.000***
Diastolic BP (mm Hg)	73.24±3.35	91.80±5.86	-18.56	0.000***
	Control (n=25)	Stage II Hypertension (n=25)	Mean difference	p-value
Vitamin D (ng/mL)	35.99±8.082	28.12±9.94	7.88	0.015*
Serum Renin (ng/mL)	3.51±3.57	8.66±6.98	-5.14	0.002**
Systolic BP (mm Hg)	110.72±5.59	144.28±19.28	-33.56	0.000***
Diastolic BP (mm Hg)	73.24±3.35	103.40±12.05	-30.16	0.000***
	Stage I Hypertension (n=25)	Stage II Hypertension (n=25)	Mean difference	p-value
Vitamin D (ng/mL)	28.71±10.85	28.12±9.94	0.59	0.975††
Serum Renin (ng/mL)	4.81±3.98	8.66±6.98	-3.85	0.024*
Systolic BP (mm Hg)	131.20±8.83	144.28±19.28	-13.08	0.001**
Diastolic BP (mm Hg)	91.80±5.86	103.40±12.05	-11.60	0.000***

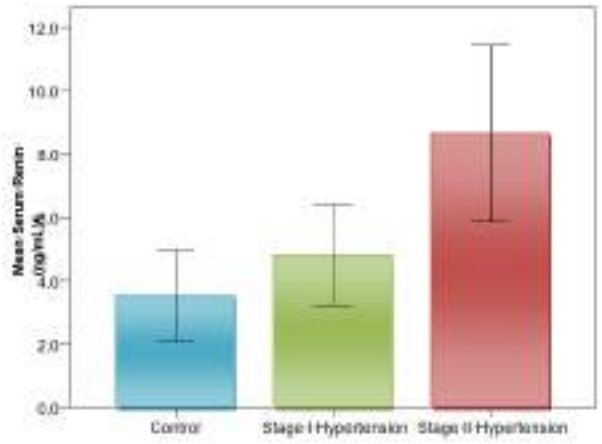
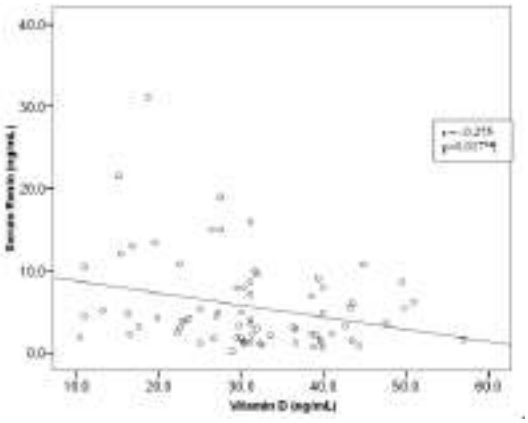


Figure No. 1: Mean Values of Serum Renin (ng/mL) levels in various groups



*= statistically significant

Figure No. 2: Correlation between vitamin D (ng/mL) and serum renin (ng/mL) in study population

DISCUSSION

High blood pressure is known for its high mortality rate[16], with an estimated 8 million fatalities each year[17]. With a prevalence rate of about 24% in adults over the age of 15, and every third person over the age of 45 suffering from high blood pressure, hypertension has invaded South Asian nations, including Pakistan.[18].

There has been much discussion about and agreement on the part of RAAS in the pathophysiology of hypertension[19] and the vitamin D-RAAS link has been studied by some researchers functioning on animals, but human evidence is scarce. We don't have any solid data, either animal or human, in this regard in Pakistan. In our research, we discovered that low vitamin D levels are linked to a high BMI, high serum renin, and high blood pressure.

The goal of our research was to see if there was a link between hypertension and low vitamin D levels, with a focus on the RAAS gene. We examined the levels of vitamin D, renin, and aldosterone in the serum of hypertensive male patients to a sample of healthy adult males.

Observational studies consistently show that serum vitamin D levels and high blood pressure have an inverse relationship. Vitamin D insufficiency was identified as an independent risk factor for the development of a cardiovascular event in the study. In 4 years of follow-up, they found that people with 25(OH) D levels less than 15ng/mL had a threefold increased chance of having high blood pressure compared to those with levels of 30 ng/mL or above[20].

In our investigation, serum renin levels were higher in participants with high blood pressure and low 25 (OH) D compared to controls with normal blood pressure and adequate vitamin D levels. Mice with the VDR gene knocked out had high plasma renin activity and high blood pressure, which could be reversed with the use of ACE inhibitors and activated 25 (OH) D3[21]. A study conducted recently showed that Vitamin D deficiency can cause over-activation of the pulmonary renin-angiotensin system (RAS) leading to the respiratory syndrome [22].

We concluded from our small study that there is a possible relationship between vitamin D deficiency and hypertension.

CONCLUSION

In hypertensive individuals, our data revealed an inverse connection between blood pressure and vitamin D, with an increase in systolic, diastolic, and plasma renin levels. Because screening for vitamin D deficiency and subsequent vitamin D supplementation is not a difficult task, it seems reasonable to test vitamin D status in regular patients in general and cardiovascular disease patients in particular.

Author's Contribution:

Concept & Design of Study:	Saima Mukhtar
Drafting:	Sara Naeem, Mah-E-Jabeen Sear
Data Analysis:	Iram Qamar, Shaista Hussain, Humaira Hashmat
Revisiting Critically:	Saima Mukhtar, Sara Naeem
Final Approval of version:	Saima Mukhtar

Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Current State of Neurosurgical Practice in Pakistan

Neurosurgical Practice in Pakistan

Priyanka Ramesh, Syed Maroof Ali, Aamir Saghir, Salman Sharif and Samir Irfan Wasi

ABSTRACT

Objective: To observe the neurosurgical facilities and patient burden among practicing surgeons in the public and private sectors.

Study Design: Prospective observational study

Place and Duration of Study: This study was conducted at the Department of Neurosurgery, Liaquat National Hospital, Karachi from 25th May 2022 to 25th June 2022.

Materials and Methods: Representatives of neurosurgical institutes throughout Pakistan filled an e-questionnaire. This e-questionnaire comprised demographic details of the hospital, outpatient and in-patient load, number of cases and equipment facilities.

Results: Data was collected from 43 neurosurgery centers. Around 1/3rd were public-sector hospitals, and approximately 1/3rd was affiliated with Medical Universities. Most of the institutes were based in Punjab (41.9%) and Sindh (30.2%). Consultant (m:1, IQ:1) to patient burden (m:100, IQ:115) was found to be steep. There was non-availability of equipment like drill, endoscope, CUSA and image-guided system in all provinces, but severe deficiency was found in one province.

Conclusion: This study shows that improvement in the overall neurosurgical setup in Pakistan is required. Our results suggest that patient burden is increasing, and there is a deficiency of neurosurgical facilities in both public and private sectors all over Pakistan. The stakeholders in Neurosurgery need to take notice and correct this promptly, with local and international help.

Key Words: Neurosurgical practice, Neurosurgery in Pakistan, Neurosurgery practice in developing country, burden of Neurosurgery in Developing countries

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INTRODUCTION

Neurosurgery is one of the younger specialties in the surgical field of practice[1]. In Pakistan, the neurosurgical practice was initiated in 1953 by Dr O.V Jooma. He was trained in England and started his practice in Jinnah Postgraduate Medical Center. A proper training program was then proposed and implemented by CPSP (College of Physicians and Surgeons Pakistan) in 1962. Since then, academic and neurosurgical clinical programs have spread throughout Pakistan.

In 2000, Pakistan had 150 practicing neurosurgeons[2]. Since then, this number has increased, and neurosurgical training has become a significant trend in surgical education.

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There have been studies in several countries to describe the past and current (including recent advances) neurosurgical practices, describing the developments, promising discoveries and areas considered for improvements. Several authors have described different aspects of neurosurgical practices in Pakistan. These include academics, surgical training, and evidence-based practice along with considerations for recent advancements (e.g., Microsurgery, Image guidance, neuromonitoring, Ultrasonic aspirators, functional neurosurgery) for better practicing surgeons[3-5]. However, the studies mentioned above have not discussed patient burden, procedure workload, and equipment advancement in institutes of Pakistan.

A specialized unit requires well equipped radiological facilities and highly effective modern surgical tools. However, several institutes lack adequate exposure and equipment for an organized neurosurgical practice.

The objective of this study was to observe the overall patient burden among practicing neurosurgeons in the public and private sectors. This study will also focus on the diversity of procedures performed in institutes of different provinces of Pakistan. The study derives from the fact that no such research has been conducted in Pakistan.

MATERIALS AND METHODS

We performed a prospective observational study after getting an approval from ethical research committee.

This study was conducted at the Department of Neurosurgery, Liaquat National Hospital, Karachi from 25th May 2022 to 25th June 2022. An e-questionnaire was sent to representatives of participating hospitals with ongoing neurosurgical practice throughout Pakistan.

We created the questionnaire using the online services of "Google Form". This online questionnaire comprised of demographic details of the hospital (province, public or private sector), university affiliation, number of consultants, number of beds and a few other queries like number of patients presenting via outpatient department (OPD) or emergency, procedures performed electively or in an emergency, and availability of radiological and surgical equipment facilities.

This e-questionnaire were sent to representative consultants of respective hospitals from neurosurgical departments throughout Pakistan via email. They were requested to fill the form via phone call (emails and phone numbers were retrieved through the database of the Pakistan Society of Neurosurgeons).

We included responses that were received within two months. Incomplete forms were excluded, and multiple responses from a single center's data were merged.

Frequencies, mean and standard deviation were calculated for all the continuous variables using IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

RESULTS

Table No.1: Institution-wise detail.

Variable	n̰ (%)
Hospital	
Government	29 (67.4)
Private	14 (32.6)
University Affiliated	28 (65.1)
Established since	
<10yrs	10 (23.3)
10-20yrs	10 (23.3)
>20yrs	22 (51.2)
Province	
Sindh	13 (30.2)
Punjab	18 (41.9)
Balochistan	2 (4.7)
KPK	10 (23.3)
Faculty	
<5 consultants	21 (48.8)
>5 consultants	19 (44.2)
Consultant	n*
Professors	39
Associate Professors	23
Assistant Professors	93

n* =number of faculty, n̰ =number of hospitals

Out of 48 institutes, 43 responses were recorded. 67% of these were public-sector hospitals, and approximately 1/3rd was affiliated with Medical Universities. Most of the institutes were based in Punjab (42%) and Sindh (30%). We also observed that almost half (51%) of the institutes are more than 20 years old, and only one-fourth of these hospitals have been established in the past 10 years. [Table 1].

Workload: The number of Professors (m:1, IQ:1), Assistant Professors (m:2, IQ:1) and Associate Professors (m:1, IQ:2) were noted to be relatively less compared to the number of patients per OPD (m:100, IQ:115) and per month (med:1000, IQ:1865) [table 2].

Table No.2: Workload.

	Median (IQ range)
Faculty	
Professors	1 (1)
Associate Professors	1 (2)
Assistant Professors	2 (1)
Residents	3.5 (21)
FCPS cleared/year	0 (2)
Surgery/year	600 (1453)
Trauma Surgery/month	35 (70)
Cranial	35 (392)
Spine	17.5 (43)
Elective Surgery/month	
Cranial	32.5 (224)
Spine	25 (116)
Vascular surgery	1.5 (9)
Endoscopic surgery	
Cranial	3.5 (21)
Spine	0 (2)
Beds	
Total beds	62 (176)
ICU Beds	8.5 (7)
OPD patients	
per month	1000 (1865)
per OPD	100 (115)
No. of drills	1 (4)
No. of Theatre	2 (2)
Weekly session	1.5 (2)

Figure No.1: Comparing Patient Burden between Provinces

Patient Burden: There was a significant difference (p=.001) in the average number of patients per OPD in

Public compared to Private hospitals (p=.001) and Sindh compared to KPK (p=.042). [figure 1,2]

Figure No.2: Comparison of Patient Burden in private & Public Hospital

Equipment Statistics: According to our data, there was non-availability of equipment like a drill, endoscope, CUSA and image-guided systems in one province [figure3]. This equipment's were widely available in all other provinces [figure 4]. We also observed the absence of vascular and endoscopic procedures in that province.

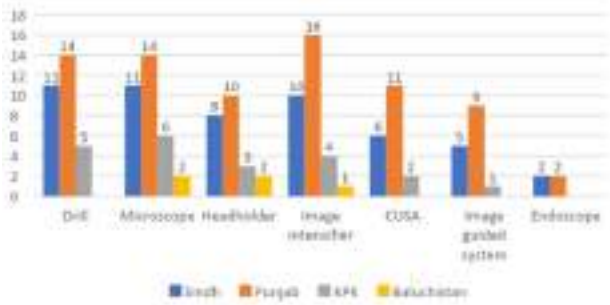

Figure No.3: Comparison of Equipment availability among Provinces

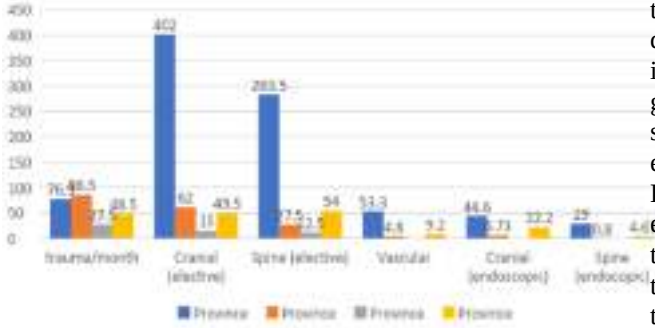

Figure No.4: Mean Operative Cases per Province

DISCUSSION

In Pakistan, neurosurgical practice started in 1951 at Jinnah Postgraduate Medical Center in Karachi due to the selfless efforts of Professor Omar Vali Jooma. He was the first to perform a thoracolumbar laminectomy for a spinal cord tumor. Later in 1956, G.D. Qazi, who had his neurosurgical training from the UK, established Pakistan's second neurosurgery center at Combined Military Hospital Lahore. In 1963, Bashir Ahmed started a neurosurgical unit at Multan[6,7]. Furthermore, the Pakistan Society of Neurosurgeons was formed in 1989. Since then, the neurosurgical fraternity has evolved tremendously.

As per our study, there are 43 neurosurgery centers in Pakistan. Among these, 28 centers are affiliated with teaching universities, and 29 are public sector hospitals. These units provide specialized care in neuro-oncology, pediatric neurosurgery, micro-vascular neurosurgery, spinal neurosurgery, endoscopic surgeries and minimally invasive procedures along with neurosurgical trauma.

We noticed that the outpatient department has a busy routine of 100 patients per consultant. 155 neurosurgeons are practicing in these centers, for a population of around 224 million in Pakistan[8]. In other words, there is one neurosurgeon for every 1.5 million persons in this country. This burden is way higher than for neurosurgeons in Turkey (1/56,000 persons), European Union (1/121,000 persons) or the United States (1/81000 persons) [9].

An average of 600 surgeries is performed per year in a neurosurgery center in Pakistan, with around 35 neurotrauma patients per month. This range is similar to the number of procedures in Ethiopia (1500 cases in 5 units)[10]. However, approximately twice these cases are performed in a large-scale center in Oslo (1000/ year) [11].

Routine elective and emergency neurosurgical procedures require specialized instruments like an electric drill, operating microscope, Mayfield head holder, image intensifier, ultrasonic aspirator, image-guided system and endoscopic system for a minimally invasive approach. Neurosurgery units in major provinces like Punjab and Sindh are well equipped with these instruments. However, we observed major deficiencies in the province of Balochistan, where there is the unavailability of ultrasonic aspirators, image-guided systems and endoscopic systems. Hence, specialized cases like microvascular surgery and endoscopic procedures are not being performed in Balochistan based centers. This lack of surgical exposure and equipment has a major negative impact on the skillset of neurosurgical residents and attending in this area. El-Fiki, an African neurosurgeon, also stated the similar scarcity of neurosurgical services and neurosurgeons available in sub-Saharan countries, compared to North and South African countries. He proposed to expand the WFNS initiative for underdeveloped countries to provide basic neurosurgical equipment at low-cost, whether public or private centers[12].

Over the past 50 years, there has been a major advancement from 3 institutes to >50 neurosurgical units in Pakistan. Most of these institutes are well equipped with modern and sophisticated diagnostic and surgical instruments for several neurosurgical disorders. Unfortunately, only 3 centers in Pakistan perform

stereotactic and functional neurosurgery, which is still limited to oncological procedures, whereas many countries like Korea, Oslo and Russia have progressed dramatically [13,14,15]. It is recommended to improve this subspecialty's expertise and equipment and introduce easy access to equipment for modern neurosurgical procedures.

CONCLUSION

We need to improve our overall neurosurgical practice in Pakistan as evident from our results that patient burden is increased and deficiency of neurosurgical facilities in both public and private sectors which will improve our outcome in these patients.

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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Career Preferences of Final Year Medical Students: A Multi-Institutional Study

Amna Ahmed Noor[1], Asad Muhammad Karim Ali[4], Gul Shaikh[5], Saman Omar[6], Saeed Ahmed[2] and Rana Tauqir Ullah Khan[3]

ABSTRACT

Objective: To investigate the various factors influencing the preference of the career in the medical students.
Study Design: Quantitative Cross Sectional Study
Place and Duration of Study: This study was conducted at the AJK Medical College (AJKMC) Muzaffarabad, Mohtarma Benazir Bhutto Shaheed Medical College (MBBSMC) Mirpur AJK, Federal Medical and Dental College (FMDC) Islamabad and Islamic International Medical College (IIMCT) Rawalpindi from October 2018 to July 2019.
Materials and Methods: Quantitative cross-sectional study was conducted by survey method to collect information by using a questionnaire developed after thorough literature search and expert validation. The reliability of the research items was tested using Cronbach's Alpha statistic. The normality of the dataset was analyzed using histograms, measures of skewness and measures of kurtosis.
Results: The results showed that 45.5% of the students preferred medicine and 16.3% of the students preferred surgery as their post-MBBS career. The preferences for other careers decreased in the following descending order: ENT, Pediatrics, Obstetrics and gynecology, Orthopedics, Anesthesia, Radiology, Eye, Pathology, Community Medicine, General Practice/Family medicine and Medical Education.
Conclusion: The findings of the study reveal that the preference of post-graduate specialization is highly skewed in favor of a few areas substantiated by the fact that 80 percent of students tend to prefer Medicine, Surgery, ENT, Pediatrics, Obstetrics and Gynecology. The study delved into the factors contributing to the preferences and choices. The identification of these factors will be helpful for the universities in formulating strategies to motivate the students to choose the ignored fields.
Key Words: Career choices, medical students, factors influencing career choices

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INTRODUCTION

Specialty career choice is a critical decision for medical students. This decision is not spontaneous for most of the students. For most, this decision is an ongoing process throughout their undergraduate schooling.

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Although some students know what specialty they want to pursue at the time of entrance, most are influenced by internal and external factors throughout their schooling. It was discussed that career choices are dynamic and likely to change over time; however, if the bias in favor of a few subject remained so, a treat of scarcity of teachers in the pre- and para-clinical departments.[1-3] It *was* identified that the career choices of medical students are biased in favor of a few departments. However, a combination of factors before, during and even after the medical course may affect the choice of a career.[4,5] It was argued that different factors persuade medical students' choice of eventual career; career inclination at the time of admission to the medical course has been a vibrant reason in this regard.[6-7] it was revealed that the students tend to select hospital medicine over general practice. It was reported that the career choices are influenced both by the graduate's inclination before starting medical school as well as the exposure during training in medical school.[8-10] Experiences in chosen specialties during training as well as the social milieu of the medical university, the teaching program and role models can influence career preferences. Societal appreciation of specialty,

specialists, response of specialty patients to treatment, and the role of specialty teachers we have conducted a multi-institutional study to identify the career choices of the final year medical students from Pakistan. Two colleges were from the public sector and two from the private sector, interestingly two are following Integrated system and the other two are following discipline based teaching system. This study is unique in a way that it is first ever conducted in the primitive area of Azad Jammu and Kashmir. We have explored some important factors influencing the future specialty preferences of these students. These identified factors can play important role in policy formation to motivate the students to choose recently ignored fields. The investigation of these identified factors when these students will start their house job or when they become medical officers needs to be followed up.

MATERIALS AND METHODS

The students surveyed belonged to four different medical colleges; AJK Medical College (AJKMC) Muzaffarabad, Mohtarma Benazir Bhutto ShaheedMedical College (MBBSMC) Mirpur AJK, Federal Medical and Dental College (FMDC) Islamabad and Islamic International Medical College (IIMCT) Rawalpindi. The students were first asked to rank the importance of different factors influencing their future career choices. Participation was voluntary and applied only to the students who were present in class on that day. The questionnaire was developed after thorough literature search and pilot testing was steered after seeking experts' validation. Students were also asked to rank the top three career choices from among 15 possible options of career specialization. They were also requested to rate the 19 chosen factors influencing their future career choices. The data was coded using like rt scale. SPSS and Microsoft Excel were used to analyze the collected data. The Cronbach's Alpha was used to measure the reliability of the research items. The level of reliability was found to be sufficient with Cronbach's Alpha value 0.691. The normality of the dataset was investigated using graphical and numerical methods. In graphical methods we used histograms of the datasets, while skewness and kurtosis measures have been used for numerical investigations. Based on these methods, it was assessed that the data are not normal. Therefore, we used non-parametric statistics such as chi square and Cramer's V statistics to analyze the impacts of the factors influencing the preference of the future profession.

RESULTS

Out of 302, 66.2% were female and 33.8% were male. 6.7% of the students were from the age group 18-20 years, 53% were from the age group 21-23 years, 38.7% were from the age group 24-26 years and 1.7% of the students were from the age group 27-29 years. On the other hand, 28.1% of the students were from Federal Medical and Dental College (FMDC), 27.8% of the students were from AJK Medical College (AJKMC), 22.5% of the students were from Mohtarma Benazir Bhutto Shaheed Medical College (MBBSMC) and 21.5% of the students were from Islamic International Medical College (IIMCT). The reliability of the questionnaire was tested using Cronbach's Alpha statistic. The Cronbach's Alpha value 0.691 indicated that the results obtained using the said questionnaire were quite reliable (Tables 1-4, Fig. 1).

Table No.1: Tendencies towards preferred careers

Preference of Career	First Choice		Second Choice		Third Choice	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
Medicine	137	45.4	28	9.3	21	7
Surgery	49	16.2	50	16.6	11	3.6
Orthopedics	13	4.3	19	6.3	13	4.3
ENT	23	7.6	33	10.9	10	3.3
Eye	6	2	24	7.9	21	7
Pediatrics	22	7.3	35	11.6	28	9.3
Obstetrics and gynecology	17	5.6	22	7.3	22	7.3
Anesthesia	7	2.3	16	5.3	14	4.6
Pathology	4	1.3	14	4.6	21	7
Radiology	7	2.3	10	3.3	32	10.6
Community Medicine	1	0.3	7	2.3	13	4.3
General Practice/Family Medicine	1	0.3	4	1.3	19	6.3
Medical Administration	0	0	3	1	9	3
Medical Education	1	0.3	3	1	14	4.6
Other	13	4.3	5	1.7	17	5.6
Total	301	99.7	273	90.4	265	87.7
Non-response	1	0.3	29	9.6	37	12.3
Overall Total	302	100	302	100	302	100

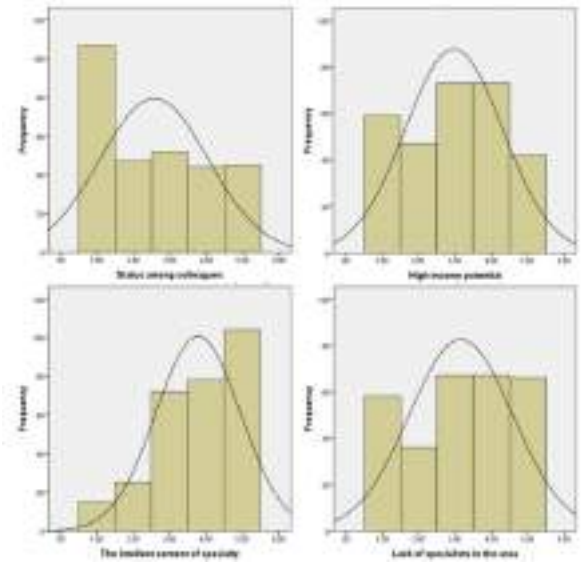

Figure No.1: Histrograms for observing normality of the datasets

Table No.2: Skewness and Kurtosis Measures to Test the Normality of the Datasets

Factors	Skewness	Kurtosis
Gender	-0.690	-1.535
Age	-0.039	-0.282
College	0.174	-1.311
First Choice	1.785	2.749
Second Choice	0.826	0.224
Third Choice	-0.016	-0.929
Status among colleagues	0.377	-1.289
High income potential	-0.097	-1.149
The intellect content of specialty	-0.684	-0.360
Lack of specialists in the area	-0.227	-1.221
Advice from parents	-0.088	-1.467
Inspired from a role model	-0.285	-1.271
Work-life balance	-0.047	-1.164
Health promotion	-0.469	-0.703
Focus on patients in community	-0.535	-0.707
Long term relationship with patients	-0.169	-1.213
Focus on urgent care	-0.522	-0.902
Results of the interventions immediately available	-0.263	-0.927
Prefer medical to social problems	-0.262	-0.931
Variety of patient problems	-0.450	-0.668
Interest in research	-0.459	-0.982
Adequate exposure to surgery	0.256	-1.949
Satisfaction of the patients undergoing surgery	0.820	-1.338
Whether surgery performance is interesting	1.161	-0.656
Change in attitude towards surgery and allied	0.806	-1.360

Table No.3: Cramer's V Statistic Values and Corresponding Interpretations

Cramer's V Statistic Values	Interpretation
below 0.15	insignificant relationship
0.15-0.20	moderate relationship
0.20-0.25	moderately strong relationship
0.25-0.30	strong relationship
0.30-0.35	very strong relationship
above 0.35	perfect strong relationship

Table No.4: Measure of significance and strengths of relationships

Preference Vs the Factors	Chi Square Statistic	Cramer's V Statistic	P-Value
First Choice Vs High income potential	70.812	0.246	0.042
First Choice Vs The intellect content of specialty	74.223	0.252	0.023
First Choice Vs Inspired from a role model	51.451	0.211	0.048
First Choice Vs Work-life balance	70.828	0.247	0.042
First Choice Vs Long term relationship with patients	64.139	0.232	0.042
First Choice Vs Focus on urgent care	71.925	0.246	0.035
First Choice Vs College	82.049	0.301	0.000
First Choice Vs Gender	23.721	0.281	0.034
First Choice Vs Adequate exposure to surgery	11.889	0.213	0.045
First Choice Vs Satisfaction of the patients	12.343	0.219	0.042
First Choice Vs Interest in surgery	22.912	0.297	0.028
First Choice Vs Change in attitude towards surgery	26.280	0.319	0.010

DISCUSSION

The surgery got second rank in the preferences as the future career followed by ENT, pediatrics, Obstetrics and gynecology, Orthopedics, Anesthesia, Radiology, Eye, Pathology, Community Medicine, General Practice/Family Medicine and Medical Education. Simply indicates a matter of concern for the other medical fields. However, in case of second option for the future career the trends have changed to a significant extent (Table 1).

It was indicated that a difference in career choice often occurs after students have completed their residency.[10-12] I have suggested that the student experiences in some subjects could be modified as an opportunity to influence students' career choices.[13-15] The more details regarding the choices of the future specialty of the medical students can be found from the contributions of the references cited therein.[16-20]

In order to ascertain the relationship between the various factors and choice of specialization, we first tested the normality of the data. Normality tests are helpful in determining if a data set is well-modeled by a normal distribution and it is the basic assumption to apply different parametric procedure to analyze those relationships. In figure.3, the histograms for the datasets regarding four factors have been presented. From this figure.3, it can be deduced that datasets are far from normality curves. The trends for the other factors were also of the similar kinds, hence not reported here individually. There are situations in which the graphical results may not clearly indicate the behavior of the data. In such situations, the numerical results are necessary to decide the normality of the data. So, we also considered the measures such as skewness and kurtosis to decide about the normality of the data. For normal dataset, the measure of skewness should be zero or close to zero and measure of kurtosis should have a value three or around three. However, from the table-2, it can be seen that there is no any combination of these measures giving values zero and three for skewness and kurtosis respectively. Therefore, these measures also indicated that the datasets are non-normal.

The table-4 shows the list of significant factors influencing the choice of the area of specialization. The significance has been interpreted in terms of the *p*-values. From the results, it is evident that all identified factors are significantly related to the varying choices of specialization. This is due to the fact that for all of the said factors the *p-values*, corresponding to the respective chi square statistic, are less than 0.05. In addition to this, we measured the strengths of influences of these factors using the Cramer's V statistic. Using Cramer's V statistic, we observed that the relationships are strong or moderately strong in most of the cases. Whereas, couple of cases provided very strong relationships.

CONCLUSION

The findings of the study reveal that the preference of post-graduate specialization is highly skewed in favor of a few areas substantiated by the fact that 80 percent of students tend to prefer Medicine, Surgery, ENT, Pediatrics, Obstetrics and Gynecology. The study delved into the factors contributing to the preferences and choices. The identification of these factors will be helpful for the universities in formulating strategies to motivate the students to choose the ignored fields.

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Original Article

Ultrasound Abdomen for Investigating Chronic Constipation and Associated Complication in Pediatric Patients

Safia Izhar[1], Samia Perwaiz Khan[2], Samreen Zaidi[3], Shazia Kadri[1], Fadieleh A. Sohail[4] and Ayesha Mir[2]

ABSTRACT

Objective: To determine the significance of ultrasound abdomen as a tool in the diagnosis of idiopathic chronic constipation, and complication in pediatric patients.

Study Design: Comparative Cross-sectional study

Place and Duration of Study: This study was conducted at the Medicare cardiac and general hospital from 25th December 2021 to June 2022.

Materials and Methods: This was an observational study. Hundred pediatric patients (age range 4-7 years) with chronic constipation, Male(n=74) to female(n=46) ratio was 3:1, visiting the Pediatrics outpatient's department and were also referred from pediatric clinics, the Medicare Cardiac & General hospital, Karachi, Pakistan Pediatric patients with complaints of chronic constipation were included in this study. Ultrasound imaging was done, and anterior and posterior imaging of the abdomen and pelvis in the supine position to visualize intestinal walls, impacted fecal material, and complications.

Results: Ultrasound imaging of the abdomen and pelvis in hundred pediatric patients with chronic constipation, findings included fecal impaction (n =89), hypermobile small bowel (n=67), worm infestation (n =31), perforation and free fluid (n =3) in these patients.

Conclusion: Ultrasound investigation was the most valuable, non-invasive tool in the investigation and management of chronic constipation in pediatric patients. Associated complications such as bowel perforation and behavioral problems were evaluated in these children by appropriate and timely management (PEG, Laxatives, Fluid and fiber along with psychotherapy etc).

Key Words: Ultrasound abdomen, FC functional constipation, Disimpaction, Laxatives, Bowel perforation, behavioral problems.

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INTRODUCTION

Constipation is a common problem in pediatric patients and may be associated with serious complications if remain untreated. The radiological investigation is the most important tool for proper diagnosis and management of serious complications associated with chronic constipation. Moreover, ultrasound imagining done early could prevent the risk of complications[1].

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Ultrasound is ideal non-invasive, safe investigation in diagnosing pediatric bowel pathology[2,3,4]. Functional constipation is reported in 95% of these cases where etiology, pathophysiology and prognosis are not well known[5-7]. Although pathophysiology of functional constipation is not certain According to Rome IV criteria it might be due to withholding habit in children[8]. Constipation is a common and prevalent condition that affects children worldwide. In Asia the prevalence of Functional constipation reported is from 0.5%-29.5%[9].

Since children are more prone to the negative consequences of constipation, it is therefore necessary to ascertain the proper medical care to improve quality of life and reduce morbidity that is associated with the condition. Idiopathic constipation can be excluded from other causes of constipation. Functional constipation is the most common presentation in children. It should also be noted that due to embarrassment associated with constipation, including but not limited to fecal incontinence only, also soiling of clothing etc., is a major factor in the reduced motivation of patients to seek assistance. Studies have shown that constipation is

associated with higher levels of stress in children[10-12] In another study, findings indicate that stressful events within a child's family circle also induce symptoms of constipation, such as divorce, death of parents etc. in about 88% of children with constipation[12]. Study done by[13] reports that children with functional constipation have behavioral problems and stress as compared to healthy controls. Another study also suggests that functional constipation is cause of emotional and social problems in children[14].

Investigation of constipation in pediatric patients with chronic constipation is abdominal radiograph or ultrasound imaging. Abdominal radiography may results in misdiagnosis, leading to frequent visits to the pediatric clinics, exposure to radiations and increased cost of diagnosis and management. Misdiagnosis can be harmful and prolong discomfort in millions of pediatric patients, thus result in recurrent multiple visits to clinic[1]. Children having abdominal pain, vomiting, constipation and diarrhea, the ultrasound is becoming a common assessment tool. In pediatric patients with acute abdominal pain ultrasound is an excellent tool to exclude any other causes of abdominal pain[2-7] .Thus ultrasound is a most convenient and accurate investigation in acute abdominal pain without any injury. B-mode and Doppler are most useful in diagnosis of underlying cause of abdominal pain. Ultrasound is a highly accurate in the diagnosis with sensitivity above 98% and specificity up to 100%-[2].This is non-invasive, with improved technology to rule out any anatomical variations, inflammatory bowel diseases or any other pathology of bowel. The imaging is performed in supine position, by using high resolution linear probe[3,5,7].

Pediatrics constipation was managed by dietary fiber and fiber supplement available over the counter along with increase in fluid intake. The addition of probiotics has been helpful in management of constipation in children [10]. Glycerin suppositories were used to soften stool in children. Laxatives or enema was used in acute cases under the under the medical advice. Deworm of the pediatric patients in case of warm infestation by albendazole or appropriate / appropriate anti-helminthic agents. Study by Cassettari et al., 2017 [11]recommended combination of green banana and laxatives to avoid complications and health issues by functional constipation. In cases of severe constipation, the patients were admitted in the hospital for short duration were prescribed enema to resolve the symptoms and severe abdominal pain. According to recommendation by NICE Guideline and ESPGHAN and NASPGHAN, increase fluid and fiber diet intake and PEG use of poly-ethylene glycol (PEG) with or without electrolytes (0.2–0.8 g/kg) (Tabber et al., 2014).[13]

MATERIALS AND METHODS

This observational study done from 25th December 2021 to 25th June 2022. Hundred pediatric patients between the age range 4-7 years with constipation and abdominal pain attending the outpatient's department and referred from pediatrics department of the Medicare Cardiac & General Hospital, Karachi, Pakistan were included in study after informed consent was taken from their parents or guardians. Abdomen ultrasound examination was performed by using Samsung HS40, examined liver, pancreas, spleen and gall bladder, urinary bladder, stomach wall for thickness and pyloric stenosis. Normal, thickness of bowel wall thickening was more than 4 mm confirmed diagnosis of bowel inflammation. Erect posture ultrasound imaging was performed to visualize free fluid and gas shadows as a finding due to perforation of bowel. By use of high resolution linear/ convex probe, normal muscularis mucosa (hyperechoic), mucosa (hypoechoic), submucosa (hyperechoic), muscularis (hypoechoic) and serosa(hyperechoic). Anterior and posterior imaging of abdomen and pelvis in supine position to visualize impacted fecal material. Erect posture imaging to diagnose free fluid and gas as are most important findings of perforation in bowel.

Inclusion Criteria: pediatric patients with chronic constipation and abdominal pain.

Exclusion Criteria: pediatric patients with any other cause of abdominal pain, inflammatory bowel diseases, spina bifida, pelvic surgery, anastomosis, hemorrhoids, diabetes mellitus.

Informed consent was taken from parents of participants. Study was approved by the ERC Sohil University (Protocol #: 000144/21)**.**

RESULTS

Hundred pediatric patients with severe or chronic constipation with or without abdominal pain were referred for ultrasound abdomen. Age range of participants was from 4-7 years. Male (n=74) and female (n= 26), ratio was 3: 1. Ultrasound images were of fecal impaction and gas shadows(dirty shadows) . Warm infestations were seen in thirty-one cases. Sluggish in case of perforation for chronic constipation. Three of these cases were referred for CT scan with ultrasound images showing perforation. All the children were recommended to increase intake of fluid and fiber in the diet. Twenty of these were prescribe lactulose and forty were given glycerin enema to relieve acute constipation. Thirty-one patients were given anti-helminthic therapy to deworm them. For children with psychosocial and stress were referred for psychotherapy. (Table 1). Ultrasound findings most frequent had fecal impaction, hypermobile small bowel. Due to fecal impaction in large bowel obstruction. Worm infestation in – cases four cases. Free fluid cases were seen were confirmed by CT scan. Sluggish movement in three cases due to perforation of the bowel. Obstruction was confirmed by the ultrasound imaging technique. Small and large bowel movements were examined for sluggish or hypermobile motility. Fecal impaction, fluid between (Graph 1) Abdominal

ultrasound images of pediatric patients (fig.1 a,b). Table -2 Management of constipation in the pediatric population.

Table No.1: General Characteristics of Pediatric patients with Chronic Constipation.

Characteristics Total no.=100	**No. Of pediatric patients With chronic constipation**
Age	4-7
Gender	M: 74 F:26 (3:1)
Clinical Findings	
Severe abdominal pain	80
Constipation	72
Loss of appetite	69
History of worm	35
Hypermobile small bowel	30

Figure No.1: Ultrasound Findings in pediatric patients

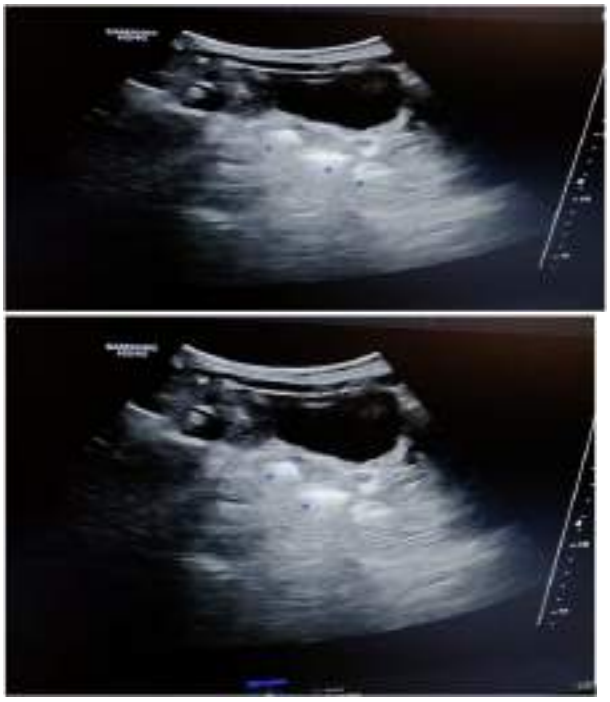

Figure No.2 (a,b): Abdominal ultrasound image, of pediatric patient with chronic constipation showing fecal impaction

Table No.2: Management of constipation in pediatric population

Fecal Disimpaction	**Doses in different age groups**
Peg 3350 + electrolytes (pediatric formula- 6.563g; NaHCO3 89.3mg; NaCl 175.4mg; KCl 25.1mg / sachet)	**<1 year -** ½ to 1 sachet
	1 – 5 years –
	Day 1 – 2 Sachet
	Day 2 and 3 – 4 Sachets daily
	Day 4 and 5 – 6 Sachets daily
	Day 6 onwards – 8 Sachets daily
	5 to 12 years –
	Day 1 – 4 Sachets
	Day 2 – 6 Sachets
	Day 3 – 8 Sachets
	Day 4 – 10 Sachets
	Day 5 – 12 Sachets (Max dose)
Osmotic laxative: Lactulose	1 month to 1 year – 2.5ml BD 1-5 year - 2.5ml to 10ml BD
	5 – 18years – 5-20ml BD
	The doses mentioned are adjusted as per the response by individual patient.
Stimulant laxative: Sodium Pico sulfate (5mg/5ml)	1 month-4 year: 2.5-10ml OD
	4-18 years: 2.5-20ml OD
Bisacodyl	2-4 years – 5-10mg OD suppository
	4-18years – 5-20mg orally, 5-10mg OD suppository
Senna (7.5MG/5ml)	2 – 4 years: 2.5-10ml OD, ½ to 2 tablets
	4 – 18 years: 2.5-20ml OD, ½ to 4 tablets
Docusate sodium (pediatric oral solution)	6months: 2 years: 12.5mg TDS
	2 – 12years : 12.5 to 25mg TDS
	12 – 18years: up to 500mg TDS
Maintenance therapy	
PEG + electrolytes	Half the disimpaction dose.

	<1 year: ½ to 1 sachet
	1-6 years: up to 4 sachet.
	6 to 12 years: up to 4 sachets.
	Dose is adjusted according to symptoms and stool consistency.
Stimulant laxative	Same as disimpaction dose
Osmotic laxative	Same as disimpaction dose
Management Given in Patients of FC	**Patients with FC (Total No=100)**
Intake of Fluids and Fiber	n = 100
Disimpaction	n= 60
Lactulose	n = 40
Enema	n = 30
Psychotherapy	n = 20

DISCUSSION

Constipation is one of the common causes of abdominal pain and frequent visits to pediatric clinics[9]. This study has shown that ultrasound abdomen investigation is most essential tool to be recommended. Ultrasound abdomen is quick, easy, cost-effective also useful in recording the bowel motility, perfusion and fluid in presence of perforation[5-6].

Patients were advise increase intake of fiber, fluid, disimpaction (n =60), lactulose (n =40), enema (n =30), anthelminthic (n = 30) and those with serious behavioral and psychological issues were referred for psychotherapy (n=20). Although functional constipation is a common problem in children worldwide with the associated issues. The research data is missing for several regions. This is a health problem resulting in frequent OPD visits, and overall physical and emotional well-being in these children. Functional complication is cause of disturbance in child's social behavior and well-being[14].

Studies [2-7] have shown that non-invasive technique of ultrasound to be highly recommended diagnostic tool for pediatric patients with chronic constipation and diagnose complications. Ultrasound imaging has found to be most useful investigation tool in investigating bowel pathology in children as it is safe, inexpensive, with no requirement of sedation or intravenous contrast. Also, with the recent advancements in ultrasound technology has improved the diagnosis[3]. It has been found rectal and radiological investigations have limitations, ultrasound abdominal examination was shown to have positive correlation [15].

Study by Nurko 2014[10], have recommended the management of functional constipation. The study suggests initiating the management by educating the patients and parents. As parents should have a positive and supportive attitude towards this issue. Change in dietary habits with increase in fluid, fiber and carbohydrates (e.g. prune, apple, and pear) improve in relief of constipation. As recommended by NICE, first step in the management is to clear the retention either via oral route of administration. Oral approach gives the child a sense of power and is the preferred method. An escalating dose of PEG 3350 (1-1.5g/kg/day for 3-6 days) is the first line with addition of stimulant if needed. In the light of available evidence, Polyethylene glycol is used as first line treatment for functional constipation in children [(NICE Guidelines 2010)[20]. Rectal approach can be used with sodium phosphate enema 2.5 mL/kg, maximum 133ml/dose for 3-6 days) if oral PEG is not available or failed to resolve. However, it is not preferred due to the fear and discomfort associated with it which can further aggravate the retentive behavior in children making constipation harder to treat. The findings in by Yoo 2017[22] study suggested combination of enema and PEG 3350 is more effective than monotherapy. Glycerin suppositories are indicated in infants for disimpaction. As maintenance therapy, once the fecal impaction has been cleared, start maintenance therapy so that the child has regular soft bowel movement. Start with half the disimpaction dose of PEG 3350 0.2–0.8 g/kg/day.

+Electrolytes or adjust as per the symptoms and response. Stimulant laxatives or lactulose can be added if PEG is not tolerated by the patient and failed to give response after 2 weeks. It is recommended to continue the maintenance dose for several weeks/months after resolution of symptoms. Many cases of re-impaction have been noted with abrupt discontinuation of laxatives. For this reason, laxatives should be gradually reduced. Appropriate and prolonged management is most essential to avoid serious complications [16-20]. Children with serious behavioral problems and stress due to functional constipation were managed by counseling the parents and involvement of child psychologist [20-22]. It has been mentioned that behavioral therapy along with laxative therapy has been suggested. The investigation for functional constipation and providing appropriate management is essential to reduce the risk of developing complication also to provide counseling to the parents and children.

CONCLUSION

All the pediatric patients with clinical findings of chronic constipation and severe abdominal pain must be recommended for abdominal ultrasound imagining in order diagnosing most serious complications such as

perforation of bowel and free fluid. Appropriate management options to avoid complications.

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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Prevalence and Predictors of Diabetes Distress among Type 2 Diabetic Patients in Southern Punjab, Pakistan

Muhammad Tahir[1], Talha Rasheeq[2], Nadeem Ullah[2], Iram Batool[3], Gohar Ali[1] and Kashif Siddique[4]

ABSTRACT

Objective: To evaluate the prevalence of diabetes distress and its associated predictors among type 2 diabetic patients in Southern Punjab, Pakistan.

Study Design: A cross-sectional study

Place and Duration of Study: This study was conducted at Endocrine Department, Nishtar Medical University and Hospital Multan from September 1st, 2020 to November 30th, 2020**.**

Materials and Methods: A sample of 152 patients from both genders were selected through non-probability convenient sampling. Only those patients whose age was above 20 years, had type 2 diabetes from the last one year and were visiting for their checkups in the endocrine department. Urdu version of Diabetes Distress Scale (DDS-17) was used to measure the diabetes distress. To see whether there was any association between the variables, both Chi-square and Pearson's correlation coefficient tests and Multiple linear regression was used to find the predictors of diabetes distress.

Results: Out of 152 participants, the majority were males, married, uneducated, unemployed, obese, hypertensive, physically inactive, and had poor glycated hemoglobin level. Among them, 66.4% participants had high diabetes distress. Multiple linear regression analysis showed that the participants' age ($\beta = .01$, $p < .05$), level of education ($\beta = .24$, $p < .05$) and glycemic level ($\beta = .12$, $p < .05$) were strong predictors of diabetes distress among the participants.

Conclusion: Diabetes distress is very common among type 2 diabetes patients, and age, level of education and HbA1c were strong predictor of diabetes distress among type 2 diabetes patients in the study.

Key Words: Diabetes Distress, Type 2 Diabetes, glycemic control, Pakistan

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INTRODUCTION

According to International Diabetes Federation (IDF), diabetes mellitus (DM) is the most common and chronic disease which affected 537 million patients worldwide in 2021 and it is estimated that this number will rise to 783 million in 2045.[1]

Pakistan has the highest comparative diabetes prevalence rate 30.8% and is included among the first three countries of the world where the highest number of adults is diagnosed diabetic being 20-79 years old.[1]

Globally, there is a rapid increase in the number of DD patients.[2] The prevalence of DD in the world varied from 8.8% to 65.5%.[3,4] Very few studies on the prevalence of DD among the patients of type 2 diabetes (T2D) have been conducted in Pakistan[5,6], one study found DD prevalence in T2D patients is 76.2%, in the capital city of Pakistan[7] it is higher than any other developing or developed country.[3,4] There is a dire need to investigate the prevalence of DD among T2D patients in any other regions of Pakistan.

Studies concluded that chronic illnesses like diabetes mellitus (DM) affects the people not only physically and economically but also psychologically. One of the outcomes of diabetes is diabetes distress (DD)[8] i.e., patient's worries about diabetes mellitus, its treatment, the need for support, and access to healthcare, is one of the emotional burdens.[9]

Diabetes distress DD has potential to aggravate the effects of DM. Inadequate treatment of psychiatric illnesses (i.e., DD) may increase morbidity and death due to poor management of diabetes (i.e., HbA1c).[10] Significant association between DD and T2D patients

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age, level of education, economic status, duration of diabetes, comorbidities, Body Mass Index (BMI), self-esteem, self-management,[5] smoking, level of physical activity and blood sugar level has already been reported.[4,5]

To find out the predictors of DD among T2D patients in Pakistan is required to fill the research gap. The aim of this study is to find the prevalence as well as predictors of DD among T2D patients in South Punjab, Pakistan.

MATERIALS AND METHODS

A cross-sectional study was conducted at Nishtar Medical University Hospital Multan, Pakistan. The research study was conducted during September 1st, 2020 to November 30th, 2020. The Institutional Ethical Review Board (IERB) issued ethical approval and informed consent was given by each participant.

Study population was T2D patients who were coming to Department of Endocrinology, Diabetes and Metabolism outpatient department (OPD), Nishtar Medical University and Hospital Multan, Pakistan. Patients who were 20 years old or more, had diabetes for the last one year were included in the study. Patients having history of mental illness, using anti-depressant drugs or diagnosed with central nervous system diseases like stroke or tumor, type 1 diabetes and pregnant women were excluded. Calculated sample size was 141 T2D patients (95% confidence level), and 76% expected prevalence of DD.[7] Estimated 10% of non-response rate was included, total sample size of 155 patients were recruited for this study.

Three senior doctors collected the data by using interviewer-administered questionnaire. Socio-demographic information and glycated hemoglobin level (HbA1c) of the patients were investigated. BMI was measured through Asian Body Mass Index and was defined as underweight- BMI <18.50 kg/m^2; Normal weight- 18.50 ≤ BMI < 22.99; Overweight- 23.00 ≤ BMI < 24.99; obese- BMI ≥ 25.00. The participants were considered hypertensive if they had blood pressure greater than 130/90 mmHg, otherwise it was 'no'.[11] Physical activity was measured according to the WHO recommendations i.e. sedentary, if the participants were not engaged in physical activity; medium, if the participants did exercise less than 150 minutes weekly; and high, if the participant did exercise 150 minutes or more weekly).[12]

To measure the DD Urdu version of Diabetes Distress Scale (DDS-17) was used.[2] DDS-17 questionnaire was validated and reliable scale to measure DD.[13,14] The alpha coefficient of the DDS-17 was 0.89. Every item of the DDS-17 questionnaire was scaled on a 6-point Likert scale from 1 (no problem) to 6 (serious problem). Glycemic control in diabetic individuals was often monitored using glycated hemoglobin (HbA1c).[15] This research had classified poor glycemic control as HbA1c levels of 7% or greater, as suggested by the American Diabetes Association recommendations.[16]

RESULTS

Statistical Package for Social Sciences (SPSS) version 22 was used to analyze the data. Frequencies, percentages, mean and standard deviation depicted descriptive data. Shapiro-Wilk test was applied for normality check of the data, Pearson correlation coefficient and multiple linear regression were also used.

The details of socio- demographic characteristics in frequencies and percentages were presented in Table 1 and Chi-square results of the study showed that the participant age, education, and HbA1c level were significantly associated with level of total diabetes distress ($p < 0.05$) (Table 1).

Figure 1 showed the prevalence of diabetes distress (DD) among participants by DDS-17 scale. Of the DD cases identified by DDS-17, 66.4% participants were found to be at high DD level, 25% participants were at moderate DD level and only 8.6% participants were at a mild level. DDS-17 sub-components- emotional burden and regimen distress of the participants had the highest level of diabetes distress 86.8% and 73.7% respectively. Pearson's correlation coefficients showed statistically significant positive correlation with participants' age, duration of diabetes and HbA1c level. DDS-17 subscales- emotional burden and regimen distress were significantly positively correlated with participants' age, duration of diabetes and BMI while physician distress was significantly correlated with HbA1c and interpersonal distress was positively correlated with participants' age (Table 2).

Table No.1: Socio-demographic characteristics and factors associated with level of DD

Characteristics	f (%)	Level of Total Diabetes Distress			Chi-square
		No distress	Moderate	High	
Gender					1.83
Male	91 (59.9%)	10 (76.9)	23 (60.5)	58 (57.4)	
Female	61 (40.1%)	3 (23.1)	15 (39.5)	43 (42.6)	
Age (years) (49.56 ±10.85)					**13.36****
20 – 40	35 (23%)	8 (61.5)	10 (26.3)	17 (16.8)	
41 – 60	99 (65.1%)	4 (30.8)	24 (63.2)	71 (70.3)	
Above 60	18 (11.8%)	1 (7.7)	4 (10.5)	13 (12.9)	

Level of education					**5.04***
Educated	82 (53.9%)	9 (69.2)	25 (65.8)	48 (47.5)	
Uneducated	70 (46.1%)	4 (30.8)	13 (34.2)	53 (52.5)	
Employment status					2.80
Unemployed	127 (83.6%)	13 (100)	31 (81.6)	83 (82.2)	
Employed	25 (16.4%)	0	7 (18.4)	18 (17.8)	
Marital Status					.354
Single	15 (9.9%)	1 (7.7)	3 (7.9)	11 (10.9)	
Married	137 (90.1%)	12 (92.3)	35 (92.1)	90 (89.1)	
Body Mass Index (27.24 ± 5.78)					3.95
Underweight	5 (3.3%)	0	1 (2.6)	4 (4)	
Normal weight	31 (20.4%)	3 (23.1)	5 (13.2)	23 (22.8)	
Overweight	26 (17.1%)	1 (7.7)	6 (15.8)	19 (18.8)	
Obese	90 (59.2%)	9 (69.2)	26 (68.4)	55 (54.5)	
Duration of diabetes (9.54 ± 6.53)					3.63
1 – 10	97 (63.8%)	11 (84.6)	26 (68.4)	60 (59.4)	
Above 10	55 (36.2%)	2 (15.4)	12 (31.6)	41 (40.6)	
Hypertensive					.061
No	74 (48.7%)	6 (46.2)	19 (50)	49 (48.5)	
Yes	78 (51.3%)	7 (53.8)	19 (50)	52 (51.5)	
Physical activity level					2.99
Inactive	100 (65.8%)	7 (53.8)	27 (71.1)	66 (65.3)	
Medium	47 (30.9%)	6 (46.2)	9 (23.7)	32 (31.7)	
High	5 (3.3%)	0	2 (5.3)	3 (3)	
Glycated hemoglobin level (8.29 ± 1.56)					**32.69****
Good (< 7)	19 (12.5%)	7 (53.8)	8 (21.1)	4 (4)	
Fair (7 – 8)	65 (42.6%)	2 (15.4)	19 (50)	44 (43.6)	
Poor (> 8)	68 (44.7%)	4 (30.8)	11 (28.9)	53 (52.5)	

*p < .05, **p < .01, ***p < .001; *f* = frequencies; DD = diabetes distress

Table No.2: Association between Diabetes Distress Scale score and related factors

Characteristics	DDS-17 score	Emotional Burden	Physician Distress	Regimen Distress	Interpersonal Distress
Age	.266**	.170*	.153	.163*	.179*
Duration of diabetes	.181*	.191*	-.051	.169*	.125
BMI	.101	.222**	.145	.354**	.154
HbA1c	.325**	-.074	-.217**	-.031	-.071

*p < .05, **p < .01, ***p < .001; Pearson's correlation coefficient

Table No.3: Multiple linear regression between glycated hemoglobin (HbA1c) and DDS-17 score

Variables	Coefficients			*t*	*p- value*
	Unstandardized Coefficients		Standardized Coefficients		
	B	S.E	*B*		
Constant	.68	.444		1.54	.127
HbA1c	.12	.033	.283	3.58	.001
Age	.01	.005	.181	2.19	.030
Gender	.05	.039	.039	.461	.646
Education	.24	.097	.180	2.40	.018
Employment status	.15	.145	.088	1.04	.297
Duration of diabetes	.13	.107	.096	1.20	.232
BMI	.01	.008	.123	1.63	.104
R^2	.22	F (7, 144) = 1.90; p < 0.001			

BMI = Body Mass Index; Multiple regression adjusted for age, gender, education, employment status, duration of diabetes, BMI.

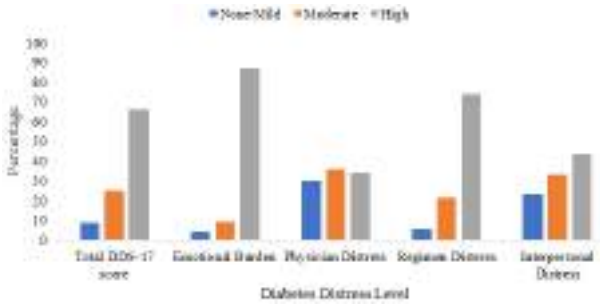

Figure No.1: Prevalence of Diabetes Distress level by DDS-17

Table 3 showed multiple linear regression analysis model, the association of HbA1c with total score of DDS-17. In the adjusted model by controlling participants age, gender, education, employment status, duration of diabetes and BMI, the regression model showed that the HbA1c was significant predictor of DD ($\beta = .283$, $p = .001$) and explained variance 22%.

DISCUSSION

The purpose of the study was to evaluate the prevalence of diabetes distress and its associated predictors among type 2 diabetic patients in Southern Punjab, Pakistan. Results revealed that majority of the participants 91.4% were suffering from DD (moderate to high) and these findings are greater than the 76.4% prevalence of moderate to high DD found in comparable local research.[7]

This study also found that emotional distress was the highest, 86.8%, followed by regimen related distress, 73.7%, interpersonal distress, 43.4%, and physician related distress, 34.5%, very similar findings were reported by one international investigation done in Canada on south Asian population and other in Pakistan which showed emotional and regimen related stress as dominant distress.[7,17]

Earlier study showed insignificant relationship between age and DD among T2D patients in Pakistan.[7] Whereas, in this study, age of the participants was significantly associated with DD, an earlier findings are in the support of these results and reported a link between age and DD.[18] Results revealed that young adults (41-60 years old) faced more DD as compared to older adults (above 60 years old).[19] Patients of a higher age reported less discomfort, which appeared to be an expected given that they already had additional comorbidities. However, younger patients were less accustomed to being unwell and had less experience managing chronic diseases than their peers. Living with diabetes required adherence to a number of daily routines that were unlikely to be accepted by younger persons.[18]

The current study showed that gender, employment status, marital status, education level, hypertension and physical activity were all determined to be insignificant predictors in DD. The previous research on the relationship between DD and these parameters had mixed results. [13,18,20] Overall, there was no statistically significant link between demographic variables and DD in investigations of rural African American women and Asian patients.[20] Other researches, on the other hand, have revealed a link between the DDS score and level of education, employment status and gender.[18,19]

Various studies reported that lower education level was associated with more DD.[18,20] Low education level was revealed to be strong predictor of high DD among participants in the current research. Low education might be to blame for the outcomes, as it led to a lack of understanding about the condition and its consequences.[21]

The present research found that the duration of diabetes and two of its dimensions (emotional and regimen-related distress) were substantially correlated with DD.[2] The study revealed that DD was higher among the participants who had fair and poor glycemic level. The study was consistent with earlier studies findings that showed that glycemic level was positively correlated with DDS-17 total score and its subcomponent physician distress.[19,21]

DD is a medically significant problem that doctors must address in order to effectively treat T2D.[22] The study recommended that enrolling people in a diabetic clinic's teaching programme improved glycemic management and was linked to a reduction in DD.[18]

The current study has some limitations. First, due to cross-sectional research design this research was done in a hospital in the public sector during COVID19. Second, there were various other factors were involved in DD and these were not considered in this study. Thus, the findings of the study was not generalized.

CONCLUSION

The study concludes that prevalence of DD is high among T2D patients. HbA1c, level of education, age, T2D duration, and BMI are significant associated predictors of DD among T2D patients in Pakistan. The findings in this research highlighting the need of clinical attention to DD, particularly in Pakistan with a high incidence of T2D and poor HbA_1c level among T2D patients.

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Original Article

Risk of Major Depressive Disorder in Adult Diabetics

Association of rs6295 with Risk of Development of Major Depressive Disorder in Adult Diabetic Population in Context of Family History of Major Depressive Disorder

Tayba Saleha Hashmi[1], Amena Rahim[2], Farhana Ayub[3], Samarah Naeem[2], Bilal Karim[4] and Jaweria Maqsood[5]

ABSTRACT

Objective: To determine whether the presence of family history of Major Depressive Disorder (MDD) is associated with the risk of development of the disease in adult diabetic population on the basis of genetic association with single nucleotide polymorphism (SNP) rs6295.

Study Design: Case control study

Place and Duration of Study: This study was conducted at the Department of Biochemistry, Islamic International Medical College Rawalpindi in collaboration with Railway General Hospital Rawalpindi, Armed Forces Institute of Pathology (AFIP) Rawalpindi and Institute of Biomedical and Genetic Engineering (IB&GE) Islamabad. Duration of study was 1 year from September 2020 to September 2021.

Materials and Methods: A total of 400 subjects were included in the study, out of which 200 were cases and 200 were age, gender and ethnicity matched healthy controls. Out of 200 cases, 100 cases had diabetes mellitus (DM) only and 100 cases had DM with MDD. Both males and females were included in the study having ages 25 years and above. Cases of both type I and type II DM were included in the study. Blood samples were collected and DNA was extracted by Chelax method. Real-time PCR was carried out to determine respective allelic frequencies of rs6295 genotype using TaqMan SNP genotyping assays and master mix.

Results: According to our results no significant association was found between rs6295 genotype and risk of development of MDD in Pakistani diabetic population in context of family history of MDD.

Conclusion: There is no significant association of SNP rs6295 of 5-Hydroxytryptamine 1A receptor gene with MDD in Pakistani diabetics having family history of MDD.

Key Words: Diabetes mellitus, major depressive disorder, 5-hydroxytryptamine 1A receptor gene, single nucleotide polymorphism, polymerase chain reaction.

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INTRODUCTION

Diabetes Mellitus (DM) and Major Depressive Disorder (MDD) are two closely associated diseases which are increasing throughout the world resulting in an increase in complications associated with diabetes. Especially this has increased the expenditure on treatment of these patients up to five-fold. MDD is because of many factors with genetic predisposition being of great importance [(1)]. The exact mechanism of development of MDD is still not completely understood. However, many theories have been hypothesized in this regard. When considering MDD in context of DM there is activation of the Hypothalamic Pituitary Adrenal (HPA) axis and the sympathetic nervous system because of chronic stress [(2,3)]. This results in increase secretion of cortisol from adrenal cortex and epinephrine and norepinephrine from adrenal medulla[(4)]. DM type 2 and metabolic syndrome ultimately result because of insulin resistance and visceral obesity resulting from chronic hypercholesterolemia and activation of the sympathetic nervous system for long period of time[(5,6)]. Hippocampus is a part of brain which is involved in both type 2 DM and depression and excessive cortisol secretion results in disturbance of the neurogenesis of

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this part of the brain [7,8]. Here also there is dysfunction of the immune system of the body resulting in an increase in the synthesis of inflammatory cytokines[9]. Ultimately there is development of type 2 DM because of the increase amounts of inflammatory cytokines which interfere with the normal functions of the β-cells of the pancreas causing insulin resistance[10].

Serotonin is a neurotransmitter involved in the pathogenesis of depression. Serotonin receptors have 14 subtypes. A single nucleotide polymorphism C(-1019)G rs6295 exists in the promoter region of the gene which encodes for one of the serotonin receptors i.e. 5-Hydroxotryptamine 1A (5-HT1A) receptor[11]. The location of this polymorphism is on chromosome number 5[12]. According to initial researches on association of rs6295 with MDD, Taro Kishi et al. found that this polymorphism is associated with MDD in Asian population but not associated with MDD in Caucasians [13].

According to Haixia Zheng et al. rs6295 allele carries a high susceptibility for MDD[14].

There is a gap in literature in this context since there is no data available about association of this specific SNP with MDD in any group of Pakistani Population[15–17].

MATERIALS AND METHODS

The study was done at the Department of Biochemistry, Islamic International Medical College Rawalpindi in collaboration with Railway General Hospital Rawalpindi, Armed Forces Institute of Pathology (AFIP), Rawalpindi and Institute of Biomedical and Genetic Engineering (IB&GE), Islamabad. It was a case control study. The research protocol was approved from the Ethics Review Committee of Islamic International Medical College, Rawalpindi. Duration of study was 1 year from September 2020 to September 2021.

In our current we have taken 200 cases (100 males and 100 females) and 200 controls (100 males and 100 females). The cases were further divided into two groups. Group 1 consisted of cases of both type 1 and type 2 DM and group 2 consisted of cases of both type 1 and type 2 DM with MDD. All the subjects were adults having ages 25 years and above. Cases of all other chronic illness and other metabolic disorders were excluded. Blood samples were collected after taking informed consent from all the subjects, following the standard techniques and then stored in EDTA bottles at 6 to 8 °C. The sampling technique was nonprobability convenient sampling. DNA was then extracted from whole blood using Chelax method and was stored at -80°C until PCR amplification. PCR was performed using original TaqMan assay (Catalog # 4351379) and master mix (Catalog # 4371353) using real time PCR following the instructions of the manufacturer.

Statistical analysis was carried out using commercial statistical software package, SPSS 26 software for Microsoft Windows. Possible association of SNP rs6295 with MDD in Pakistani diabetics was determined by computing odds ratio (OR) and 95% confidence intervals (CIs). Frequencies and percentages were determined for descriptive statistics. *p*-value less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

There were 200 cases and 200 healthy age, sex and ethnicity matched controls. Out of 200 cases, 100 cases had DM and 100 cases had DM with MDD. In the group having positive family history of MDD, among 100 cases of DM 4 (1.0%) none had CC, CG or GG genotype. Among 100 cases of DM with MDD 7 (1.8%) had CC genotype, 5 (2.2%) had CG genotype and 0(1.3%) had GG genotype. In Controls, out of 200 subjects 2(10.0%) subjects had CC genotype, 11(16.9%) subjects had CG genotype and 3 (7.7%) subjects had GG Genotype.

Table No.1: Association of 5-HT1A receptor gene SNP rs6295 Genotype with family history of MDD in cases and controls

Parameter	N=400			OR (95% CI) P
	Cases n=200		Controls n=200	
Family History of MDD	DM n=100	DM with MDD n=100		(*P ≤ 0.05)
Present				
CC	0(0.00%)	7(1.75%)	2(0.50%)	Ref I -[a] -[a]
CG	0(0.00%)	5(1.25%)	11(2.75%)	Ref I -[b] -[b]
GG	0(0.00%)	0(0.00%)	3(0.75%)	Ref I 0.13 (0.02-0.86) -[c] -[c]
Absent				
CC	28(7.00%)	30(7.50%)	61(15.25%)	Ref I 1.73 (0.89-3.38) 0.106[a]
CG	55(13.75%)	34(8.50%)	92(23.00%)	0.75 (0.33-1.72) 0.478[a]
GG	17(4.25%)	14(3.50%)	31(7.75%)	Ref I 1.30 (0.74-2.28) 0.354[b] 0.92 (0.46-1.81) 0.806[b] Ref I 0.75 (0.42-1.35) 0.340[c] 1.22 (0.58-2.57) 0.597[c]

[a] – Association of genotype of group DM and group DM with MDD
[b] – Association of genotype of group DM and Controls
[c] – Association of genotype of group DM with MDD and Controls

In group having no family history of MDD, among 100 cases of DM 28 (6.0%) had CC genotype, 55 (10.7%) had CG genotype and 17 (4.3%) had GG genotype. Among 100 cases of DM with MDD 30 (7.5%) had CC genotype, 34 (10.0%) had CG genotype and 14 (2.2%)

had GG genotype. In Controls, out of 200 subjects 61 (5.8%) subjects had CC genotype, 92 (8.8%) subjects had CG genotype and 31 (0.8%) subjects had GG Genotype.

DISCUSSION

DM and depression have common pathological pathways[18]. Presence of DM ultimately results in MDD and presence of depression ultimately causes DM[18]. The presence of one causes another[19]. The presence of depression with DM worsens the compliance and patient's glycemic control resulting in serious complications of DM including cataract, retinopathy, nephropathy and neuropathy etc.[20,21]. Therefore, in order to keep DM under check it is very necessary to evaluate all the suspected patients for MDD. Timely referral to psychiatrist and early start of treatment of MDD can work miracles when it comes to treatment of diabetes, as it is true for the treatment of many other chronic diseases.

To the best of our knowledge this is the first study to be conducted in Pakistan using this SNP rs6295. This SNP is known for causing MDD[22]. As we already know that genetic studies are the most advanced field of research in medical and health sciences and give details of a disease at the molecular level so findings of such studies are very reliable if genotyping is performed on modern techniques. For this purpose, work has been done using original TaqMan genotyping assay and original TaqMan genotyping master mix using real-time PCR technique.

According to literature so far very limited work has been done in Pakistan when it comes to genetic studies regarding depression. Here we have taken both type 1 and type 2 diabetic patients who were all adults having ages 25 years and above. We have tried to find the genetic association of this SNP with the family history of major depressive disorder. No significant association of rs6295 genotype and risk of development of MDD has been determined with respect to family history of MDD in our diabetic population. In the context of genetic diseases not finding a significant association is also important. This means that the population under consideration is less likely to develop the disease which in this case is MDD. However according to M. Dijk et al, who conducted a study on the population of United States there is an increased risk of development of MDD in children whose parents are affected with the disease[23].

CONCLUSION

No significant association was found between rs6295 genotype and risk of development of MDD in context of family history of MDD.

Recommendations: In our current study we have taken into consideration SNP rs6295 and we have tried to determine its genetic association with risk of development of MDD in context of family history of MDD. In future, other similar SNPs can be taken into consideration and combination of two or more SNPs can be taken into consideration for more elaborated results.

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Original Article

Assessment of Knowledge and Attitude Regarding Dietary Items among Diabetic Patients

Mohsin Khan[1], Abdul Rauf[1], Niama Khan[2], Iqra Jadoon[1], Junaid Khan[1] and Faiza Khan[3]

ABSTRACT

Objective: To improve the quality of life for diabetic patient, but doing so necessitates that these individuals get the necessary information and abilities to manage their everyday lives care. Deciding on meals and eating routines are affected by the patients understanding of diet.

Study Design: Cross sectional study

Place and Duration of Study: This study was conducted at the Ayub Teaching Hospital Abbottabad from May 2022 to July 2022.

Materials and Methods: The term knowledge means medical knowledge about particular dietary items. Regular is defined as ≥ 4 days a week or >16 days a month. Critically ill diabetic patients were excluded from study.

Results: 200 patients with mean age of 59.07 were included in present study. The mean systolic blood pressure was recorded as 136 mm of Hg and mean diastolic BP was recorded as 84mmHg. 74 individuals are overweight and 61 are obese. Medical knowledge about vegetables was observed in 92 subjects, 42 used fruits, 85 used white wheat and 34 used brown wheat regularly. 47 used sugars regularly despite medical knowledge. 59 participants lacked knowledge about whole meat and meat without fats. 146 had knowledge about benefits of unsaturated fats but only 91 practiced regularly in their diet.

Conclusion: Participants significantly lacked medical knowledge about vegetables, fruits and white wheat. Respondents having significant medical knowledge practiced regular usage of brown wheat and low consumption of sugar and gur/shakkar. Majority of participants did not consumed meat because they belonged to uneducated group and had very poor income. Respondents had significantly good knowledge about fats but less than half of participants consumed unsaturated fats regularly in their diet.

Key Words: Knowledge, Dietary items, Body mass index, Education

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INTRODUCTION

Diabetes mellitus and hypertension are the two most important non communicable diseases responsible for high mortality worldwide. There is a rising trend of diabetes in both developing and developed countries[1,2]. Diabetes is a lifelong disease with an increased risk of premature deaths as well as acute and chronic complications[3,4].

Diabetes mellitus (DM) is described by the World Health Organization (WHO) as "a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with change in the metabolism if carbohydrates, fats and proteins as a result if defects in insulin secretion, action of the insulin, or both[5]. The treatment of diabetes is mainly through drugs or lifestyle modifications. Among the modifiable risk factors, careful dietary habits are one of the very effective ways to control diabetes as unhealthy eating habits are one of the major reasons for hyperglycemia. Moreover, adhering strictly to a restricted diet along with regular physical exercise reduces the number and doses of antidiabetic drugs, and in certain cases may be sufficient to control diabetes alone. The patient should have adequate knowledge and strong motivation to observe healthy food practices. Pan et al figures indicate that about 31% to 46% of diabetes can be avoided by the regular use of vegetables and fruits, reduced use of saturated fats, sodium, and refined sugars, by increasing physical activity and controlling smoking habits[6].Low carbohydrates diets are effective way of improving HBA1C and its also reduces obesity, proven by various RCT trials[7,8]. Hyper caloric diet and, western dietary styles also increasing the prevalence of diabetes mellitus in younger age[8,9] group.

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The Hazara region is a northern part of KP comprised of 6 districts (Haripur, Abbottabad, Mansehra, Batgram, Kohistan, and Torghir) and Ayub Teaching Hospital (ATH) is a referral center for them. The people of this region have their own culture and eating habits. The present study is therefore designed to assess the knowledge and attitude towards healthy and unhealthy eating habits in the diabetic population of our area, this will not only help to increase the awareness about dietary habits but will also help the patients to observe healthy food practices[10].

MATERIALS AND METHODS

This will be a cross-sectional study that will be carried out on diabetic patients admitted in the medical units of Ayub Teaching Hospital Abbottabad. A total of 200 diabetic patients will be included in the study. A brief demonstration will be conducted for data collectors and food items which are healthier for diabetes like complex carbohydrates, unsaturated fats etc. were defined and explained to researcher. The term knowledge means retrospective patient medical knowledge about particular food item which he gains from his physician, dietician etc. The regular means consumption of food four are more than four days in a week or consumption of food item 15 or more than 16 days in a month. The income group from 5 thousand to 25000 included very poor category, income group from 30000 to 50 thousand is Borderline group (poor), and income with 51000 to 1 lack is satisfactory, over 1 lack belongs to rich category. Underweight was defined as < 18.5kg/m^2, normal weight as 18.5 to 22.9, overweight as 23 to 24.9, and obese as ≥ 25[10]. The data collectors recruited to cardiology, endocrinology, gastro-enterology and medical units to collect the data from diabetic patients. The study was conducted from 1st May2022 to 15 July 2022 in Ayub teaching hospital Abbottabad.

Critically ill patients and those having serious comorbidities like congestive cardiac failure, end-stage renal disease will be excluded from the study. The information regarding dietary habits will be collected by a personal interview on a pre-designed questionnaire. The data obtained will be analyzed by using SPSS software version 21.

RESULTS

About 200 diabetic patients, age range from 16 to 106 years were included in the study. The mean age of respondents was 59.07±13.1 among which 48.5% (97) were males and 51.5% (103) were females. 42% (84) were residents of Abbottabad, 28.5% (57) from Manshera,10.5% (21) from Batagram,7.5% (15) from Haripur, 5.5% (11) from Kohistan and 6% (12) belonged to other regions. Regarding education 58% (116) were uneducated and 53.5% (107) belonged to urban areas. The mean systolic blood pressure was recorded as 136± 17 and the mean diastolic pressure recorded as 84±10, detail of demographic variables is shown in Table1.

Table No.1: Showing Demographic Characteristics

Variables		**Total No**
Body mass index (BMI)	<18.5	07
	18.6-23.0	58
	24-27.4	74
	≥27.5	61
Income	5000-25000	100
	30000-50000	31
	51000-1lack	63
	Not mention	06
Occupation	Nothing	54
	Office job	10
	Manual worker	28
	House wife/worker	92
	Businessman	05
	Not disclosed	11
Current Smoking status	Yes	15
	No	81
	Refusal	104
Education	Uneducated	116
	Primary	37
	Secondary	42
	Graduation	05
Dietary advisor	Dietician	02
	Physician	127
	Family member	56
	No advisor	15
Duration of Diabetes	1-10years	125
	11-20years	57
	>20years	17
Physician visits	weekly	02
	Monthly	30
	Yearly	53
	No follow-up	115

Table No.2: Dietary Knowledge of Participants

Diet [Regularly means consumption ≥ 4 days in a week, while never means 1 or No use in a week] (n=200)		Knowledge		P-Value
		Yes	No	
Vegetables	Regularly (125)	98	27	0.006
	Never (75)	45	30	
Fruits	Regularly (51)	42	09	0.02
	Never (149)	97	52	
White Wheat	Regularly (160)	85	75	0.00
	Never (40)	35	05	
Brown Wheat	Regularly (42)	34	08	0.001

	Never (158)	84	74	
Maize	Regularly (07)	02	05	0.445
	Never (193)	96	97	
Barley	Regularly (00)	00	00	-
	Never (200)	77	123	
Sugar	Regularly (58)	47	11	0.00
	Never (142)	138	04	
Gur/ Shakkar	Regularly (13)	03	10	0.001
	Never (187)	131	56	
Carbonated drinks	Regularly (03)	03	00	0.62
	Never (197)	166	31	
Sugar free drinks	Regularly (01)	00	01	0.4
	Never (199)	108	91	
Whole meat	Regularly (12)	08	04	0.751
	Never (188)	133	55	
Meat without fats	Regularly (09)	06	03	0.156
	Never (189)	143	46	
Saturated fats	Regularly (77)	41	36	0.000
	Never (121)	105	16	
Unsaturated fats	Regularly (105)	91	14	0.000
	Never (95)	55	40	

DISCUSSION

Very little literature exists on the knowledge about dietary items among people with diabetes mellitus in Pakistan. Studies which are available about knowledge, beliefs and practices are deficient in highlighting patient's knowledge about dietary items[11-14]. Akber N et al highlighted carbohydrates, proteins and fats in journal but study lacks specific basic dietary items[15].

The mean age of respondents was 59.07 years which is slightly older than study done in Karachi by Rafique G et al and Patel M et al[16] but consistent with FA Olatona et al[17]. The reason could be that most of our patients are inpatients which are admitted for various comorbidities. Male to female ratio is almost consistent with that reported by Rafique G et al. More than half (58%) of participants were illiterate which is coherent with that reported by Gul N et al. Rafique et al reported 14.6% illiteracy ratio in diabatic participants which is quite lower than our figure. Most of our participants (58%) belonged to far flange rural areas, this could be the reason of higher ratio of illiteracy. The mean systolic blood pressure was recorded as 136±17 and mean diastolic pressure was 85±10 which fall near to the patients who are taking drugs, as reported by Patel M et al. We recorded those 135 (67%) patients had BMI over than recommended (18.6-23.0), FA Olatona et al reported 74%. Patel M et al reported that 76% patients had higher BMI than normal, the difference may be due to small sample size of over study.

125 participants regularly ate vegetables, 57 had no medical knowledge about importance of vegetables in diabetic diet (P=0.006). 43 participants who never used vegetables belonged to low-income group (P=0.05). 51 participants used fruits regularly, only 42 had medical knowledge about fruits beneficial for diabetics (P=0.02). 149 never used fruits regularly because majority of them were uneducated (P=0.027). 160 used white wheat regularly, half had no knowledge about regular use of white wheat (P=0.00) and 100 of them also belong to uneducated group (P=0.06). 42 used brown wheat and 34 of them had medical knowledge (P=0.001). Among 158 who did not used brown wheat 99 belonged to uneducated group (P=0.07). 193 never used maize 102 did not had any knowledge about its benefits (P=0.445). 96 who did not used maize regularly were very poor but difference was not significant (P=0.26). 185 had knowledge about sugar. 142 never used sugar regularly in their diet with significance of 0.00. 134 had knowledge about gur/shakkar (brown sugar) only 13 practiced regularly with significance of 0.001.

188 never used whole meat regularly in their diet among which 97 belonged to very poor income group (P=0.02) and 133 were related to uneducated group (P=0.02). No significant difference was observed when compared with medical knowledge about consumption of whole meat (P=0.75)

Only 41 respondents used saturated fats regularly and 146 had good medical knowledge about it with significance of 0.00. 91 participants regularly used unsaturated fats and 54 are unaware of its medical importance with significance of 0.000.

CONCLUSION

67% participants had BMI greater than recommended. 50% diabetics belong to very poor group of income. Participants significantly lack medical knowledge about vegetables, fruits and white wheat. Regular usage of brown wheat and low consumption of sugar and gur/shakkar was done by the respondents who had significant medical knowledge. Respondents lacked medical knowledge about maize but no significant cause was observed. Majority of participants did not consumed meat because they belonged to uneducated group and had very poor income. Respondents had significantly good knowledge about fats but less than half of participants consumed unsaturated fats regularly in their diet.

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Original Article

Effectiveness of Educational Program on Self-Management Behaviors of Asthmatic Patients

Self-Management Behaviors of Asthmatic Patients

Sidra Nadeem[1], Muhammad Afzal[1], Adnan Yaqoob[1] and Sadia Khan[2]

ABSTRACT

Objective: To evaluate the effectiveness of educational program on self-management behaviours of the asthmatic patients.

Study Design: Quasi experimental study

Place and Duration of Study: This study was conducted at the Rehmat Ward, DHQ Hospital Faisalabad from 1st May 2020 to 31st October 2020.

Materials and Methods: Thirty six patients were enrolled by using purposive sampling technique in current study. After taking the consent all the mild to moderate asthma patients of both genders were controlled in current study. Educational intervention was provided for 4 months from their day of admission to discharge and follow up visit at chest department. Patients knowledge and self-management behaviour was assessed by asthma Self-Management Behaviour measures Questionnaire (ASMQ) and the Asthma Quality of Life Questionnaire (AQLQ).

Results: The findings of current study reveal that out of 36 participants 17 were between the age group 15-30 years and 19 were in the age from 31-60, majority 24 (66.7%) patients were male and 41.7% have completed their education till middle. The findings showed that there was a significant difference between the pre and the post interventional knowledge's score (16.0 vs 24.5), Quality of life (63.0 vs. 28.5) and self-management behaviour (27.0 vs. 23.5) among patients (p value <0.001).

Conclusion: The educational intervention appears to be an effective method to improve asthma control self-management behaviours, disease knowledge, quality of life, and self-efficacy in asthma patients.

Key Words: Asthma, Intervention programme, Education, Self-management skills

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INTRODUCTION

Asthma is most severe chronic illness among all diseases and the leading cause of disability and morbidity affecting all age group worldwide. There is an increase of global prevalence of allergic diseases which results in increase economic burden.[1] Asthma has affected all age groups, which is almost 334million population across the world. According to research asthma case prevalence has reported greater times it has been estimated that asthma patients will be increased by 100million globally by the year of 2025.[2]

In China, the incidence of asthma was 4.2%, which is generally 45.7% population in which 1.1% population which is account for 13.1 million is adults and has air flow limitation due to under diagnosed and under treatmemt.[3]

The prevalence of adult self-reported asthma is around 1.8 per cent, according to the Indian National Family Health Survey.[4] Asthma prevalence estimates in Pakistan at 4.3% in the global asthma burden report. Asthma prevalence in Asia has been shown to range from 0.7% to 11.9 % but there were also significant differences in the definition of asthma.[5] The triggering stimuli such as smoke, dust, pollens, cold and hot food items, tobacco, extraneous exercise, perfumes, pet dander, humidification in air, emotional instability causes hypersensitive to airway. When the patients is exposed to theses triggers the patients suffers severe asthmatic attack in which airway inflamed followed by spams, shortness of breath, cough and other symptoms occurs.[6]

Knowledge is the acquisition of behavioral change, knowledge, skills and attitudes by learning as an action and process. Improving the patient's quality of life is the major concern in chronic disease. Asthma control approaches not only concerned with recovering patients vital functions such as improving breathing circulation and managing airway but also enhance their quality of life by restricted adherence to disease triggering stimuli.[7] Lack of knowledge, poor self-management skills are contributing factors of severity among

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asthmatic patients. No doubt effective medicines and treatment cover the symptoms but in some cases resistance develop due to disease severity, patients adherence to prescribed treatment and lack of awareness about disease.[8] A study conducted by Gree (2017) has confirmed that, although people with asthma strongly want to know about their disease, they do not want to take the lead decisions in exacerbation. For health professionals, this presents a problem because the most recent guidelines recommend greater autonomy in decision making with the help of written action plans for patients.[9] There was an evidence of successful and effective self-management programs implemented in other nations, such as Australia, that focused on the important role of effective education can play in decreasing asthmatic symptoms and consequently reducing doctor visits.[10] Effective education provided by nurses to patients suffering with asthma should focus on enabling these patients to improve their knowledge, practices, and asthmatic control measures and enhance their awareness of how to avoid triggers of asthma attacks.[11]

The asthmatic patients have no knowledge regarding asthma self-management. Poor understanding regarding disease control can results in underutilization of healthcare facilities and increase disease mortality and morbidity and financial burden. Both the nurse as well as patients plays a vital role for the management of the disease. Thus, there is need for nursing intervention program to provide and improve basic patient's knowledge regarding self-management behaviors to improve the quality of life of patients with asthma and lessen the severity of symptoms and reduce the burden of disease. Therefore this study was conducted to evaluate the effectiveness of educational program on self-management behaviours of the asthmatic patients.

MATERIALS AND METHODS

This quasi experimental study was conducted at Rehmat Ward, DHQ Hospital Faisalabad. A total of 36 patients were enrolled by using purposive sampling technique in current study. After taking the consent all the mild to moderate asthma patients of both genders were controlled in current study. The exclusion criteria were medical students and professionals, comorbidities like heart disease, kidney failure, pregnant females, or patients currently taking any psychotic medication along with asthma. The data was collected from asthmatic patients from chest ward of DHQ hospital Faisalabad. Researcher keeps in contact to patients during the hospital stay and after discharge through a weekly meeting in conference room of ward and through telephone for any information and caring for asthma at home. Educational intervention was provided for 4 months from their day of admission to discharge and follow up visit at chest department. Patients were guided to fulfil the educational requirements. Patient's demographic data was collected. Asthma Self-Management Behaviour measures Questionnaire (ASMQ) adopted tool consists of 30 items, which measures the control of asthma was assessed by patients' response 1 as very often, 2 as sometimes, and 0 as never. The correct response was marked as "1" and incorrect response was marked as "0". The level of knowledge was further be classified on the base of score obtained, Poor knowledge <50%, Moderate knowledge: 51-75%, Adequate knowledge: >75% and the Asthma Quality of Life Questionnaire (AQLQ) tool contains 20 items was used to assess the asthma-related quality of life. The participants quality was assessed by rating 1 as not at all, 2 as mildly, 3 as moderately, 4 as severely and 5 as very severe and quality was be described as poor, average and good. The participants quality was be described as poor, average and good. It was categorized a Poor Quality: <50%, Fair Quality: 51-70%, Good Quality: >75%. These tools were developed by Mancuso CA, in 2009 used to assess patient's knowledge and Quality of life.[12] After 4-month intervention the same questionnaire, used to collect post intervention data.

Phase I: Intervention was divided into 2 phases. In first phase the participant was introduced about the program after the self-introduction of researcher. Written and informed consent was taken and patient demographic data was recorded.

Phase 1I: The pre intervention data was assessed through structured schedule questionnaire. Patient's self-management behaviours were assessed using Asthma Self-Management Questionnaire (ASMQ), asthma quality of life questionnaire was used.

Phase III: In phase III patients were given intervention through educational programme which lasts for 16 weeks. The duration of each session ranged between 30-45 minutes. At the beginning of each session researcher starts by giving a summary about previous session and explaining the objective new one. Different strategies were used including brain storming, instructions, lectures, role play and group discussions. After 4-month of intervention post-test data was collected through same instrument. Intervention was developed by a book publish by Registered Nurses' Association of Ontario in 2017, with the title of Adult Asthma Care: Promoting Control of Asthma. [13]

Data was entered and analysed by using SPSS version 21. Frequencies and percentages were calculated for demographic data such as gender, age, occupation, disease onset, educational level, smoking history and housing condition. Dependent t-test was applied to find the mean differences of e self-management behaviours of asthmatic patients before and after the intervention. Differences was considered statically significant if $p \leq 0.05$.

RESULTS

Seventeen were between the age group 30-45 years and 19 were in the age from 46-60. Majority of the participants were males 24 (66.7%). 41.7% participants were having middle education level, whereas only 3 participants have completed their matriculation. Moreover, the remaining 13 (36.1) participants were illiterate and 5 (13.9%) having primary level of education. Only 4 (11.1%) who were not working whereas 20 (55.6%) and 12 (33.3%) were labors and drivers respectively. 52.8% of the participants never smoked while 33.3% smoke sometimes and 13.9% smoke very often. The majority of the patients were suffering from more than 6 months 61.1% and almost 58.33% were living in congested and non-cemented house while 41.7% were having well ventilated and cemented house (Table 1).

Table No.1: Demographic variables of the study participants (n=36)

Variable	No.	%
Age (years)		
30 – 45	17	47.2
46 – 60	19	52.8
Gender		
Male	24	66.7
Female	12	33.3
Education		
Primary	5	13.9
Middle	15	41.7
Matric or above	3	8.3
Illiterate	13	36.1
Occupation		
Labourer	20	55.6
Driver	12	33.3
Do not work	4	11.1
Smoking Status		
Never	9	52.8
Sometime	12	33.3
Very often	5	13.9
Asthma Duration		
3 to 6 months	14	38.9
> 6 months	22	61.1
Housing Condition		
Well ventilated and cemented house	15	41.7
Congested and non-cemented	21	58.3

Table 2 indicates that in the pre-interventional phase the majority of the participants 32 were having poor knowledge while only 4 participants were having the moderate knowledge. The findings showed that there was a significant difference between the pre and the post interventional knowledge's score among participants regarding the asthmatic self-management behavioras evident by p<0.001. Moreover, when self-management behavior is categorize into uncontrolled, partial and controlled behavior; results shows that in both pre and post group none of the participant showed the controlled behavior. In pre group majority of the participants showed the uncontrolled behavior 97.2% while in post group the patients showed the uncontrolled and partial behavior as 38.1% and 61.1% respectively. The findings revealed that there was a significant difference between pre and post interventional score of self-management behavior among participants as evident by p<0.001.

Table 2: Comparison of pre and post knowledge and self-management behavior categories

Variables	Pre-intervention	Post-intervention	z-value	p-value
Knowledge				
Poor	32 (88.9%)	5 (13.9%)	-5.076	< 0.001
Moderate	4 (11.1%)	8 (22.2%)		
Adequate	-	23 (63.9%)		
Self-Management Behavior				
Uncontrolled	35 (97.2%)	14 (38.1%)	-3.854	< 0.001
Partial	1 (2.8%)	22 (61.1%)		
Controlled	-	-		

DISCUSSION

Asthma regular care is thought to include an important role for self-management education. The failure to utilize human behavioral processes and motives in operating educational programmes is related to the failure to train patients for managing chronic diseases. Therefore, to improve the efficacy of educational interventions for self-management, effective behavioural techniques are required. [14]Therefore the objective of the study is to evaluate the effectiveness of educational program on self-management behaviours of the asthmatic patients.

In the present study educational intervention was provided for 4 months from their day of admission to discharge and follow up visit at Chest Department. Patients were guided to fulfil the educational requirements. Patient's demographic data was collected. Asthma Self-Management Behaviour measures Questionnaire (ASMQ) the Asthma Quality of Life Questionnaire (AQLQ) tool were used. Pre and post intervention data was collected. The findings of current study reveal that out of 36 participants 17 were between the age group 15-30 years and 19 were in the age 31-60, majority 24 (66.7%) patients were male and 41.7% have completed their education till middle.

According to the National Health Interview Survey, 13% of children aged 0 to 17 in the United States had asthma at some point in their lifetimes in 2007. Children (9.5%) have a greater annual prevalence of asthma as compared to adults (7.7%).[15] Around 14% of children worldwide have asthma, and in adult population, this is increasing. Particularly among lower socioeconomic levels with less access to appropriate

treatment, asthma is a serious domestic and worldwide health issue that is now rapidly increasing.[16]

In this study knowledge of self-management behavior of patients were also observed. The findings showed that there was a significant difference between the pre and the post interventional knowledge's score and self-management behaviour among participants regarding the asthmatic self-management behavior as evident by (p value <0.001). Furthermore, there was a significant increase in the median knowledge scores, after the intervention with median difference was 8.5 from the pre-scores.

A pilot randomized controlled trail was conducted on the WEB-BASED Asthma self-management system. The objective of the study was to compare the web-based asthma control system and usual care on asthma control, behavior, knowledge and quality of life among patients. Patients were divided into two groups. Group A was given web-based intervention and group B usual care. The results of study revealed that the from baseline to 3 months intervention there was significant improvement in quality of life, self-reported symptoms, knowledge and behavior in web-based asthma control program as compared to control group.[17] Similar to our findings, a recent evaluation of systematic reviews revealed that the studies conducted on an adult population preferred the web-based intervention on asthma-related quality of life as well as on self-reported symptoms and asthma control. Self-reported asthma control frequently overstates the impact of therapies, according to prior research.[18]

Another study was conducted in 2021 on educational program on asthma patients. The results showed that in terms of asthma control, asthma self-management, and asthma knowledge and awareness, patients in the intervention group showed significant improvement than control group. Patient activation was very high in this group. These findings also support the current study which shows significant improvement in self-management behavior, knowledge and quality of life among asthma patients.[19]

A nurse led asthma control intervention study was conducted for school going children. It was reported that there was significant improvement in the knowledge of asthma symptoms and daily activities at 6 and 12th week follow-up. For school-aged children with asthma, self-management is a challenging task, but nurses can offer essential learning opportunities and continuity of care.[20]

A quasi experimental study was conducted on self-management behaviour on asthma patients to evaluate the effect of educational program. 103 patients were enrolled in study the results showed the significant improvement before and after intervention. Patients showed 49.5% controlled behavior as compared to baseline data. The study concludes that these educational programme have significant impact on patients behavior.[21]

CONCLUSION

The educational intervention appears to be an effective method to improve asthma control self-management behaviours, disease knowledge, quality of life, and self-efficacy in asthma patients. A better understanding of the differences between knowledge and behavior and the factors that affect them could result in asthma educational interventions that are more successful. By encouraging and supporting changes in health behavior, giving patients with chronic diseases timely access to health information and individualized notifications when action is required may enable people to self-manage themselves more effectively.

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Original Article

Under-Nutrition Among Children Under Five Years

Socio-Demographic and Child Caring Factors Responsible for Under-Nutrition among Children between 6-59 Months in Sindh, Pakistan

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ABSTRACT

Objective: To determine the association between socio-demographic and child related factors with under-nutrition among children having age between 6-59 months in Hyderabad, Sindh.

Study Design: Cross-sectional study

Place and Duration of Study: This study was conducted at the Pediatric department, Liaquat University Hospital Jamshoro from August 2020 to February 2021.

Materials and Methods: Children belongs to either gender, aged between 6–59 months were included. Socio-demographic profile of child as well as parents and child's caring practices was recorded using a semi-structured written questionnaire.

Results: Total 384 children included while mean age of participants was 24.4±11.4 months. Prevalence of stunting, wasting and underweight were 52.6%, 17.2% and 30.2% respectively. A statistically significant association ($p<0.05$) between different factors with the nutritional status of children include child age, birth order, diarrheal and measles morbidity, parental education, father occupation, family income, house type, health seeking behavior and vaccination.

Conclusion: Prevalence of under-nutrition is high in Hyderabad. Child age, birth order, diarrheal and measles morbidity, parental education, father occupation, family income, house type, health seeking behavior and vaccination are associated with the nutritional status of children.

Key Words: Malnutrition, Nutritional status, Stunted

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INTRODUCTION

Malnutrition is a critical global public health problem a fundamental cause that contributes considerably to morbidity and mortality among children that is induced by a number of interconnected variables. Under-nutrition endangers children's physical and cognitive development, increases infection risk, effecting school performances and effecting physical work capacity. Nearly half of all children deaths around the world resulting from the under-nutrition.[1-3]

Globally, over 2 billion people are affected by malnutrition. Roughly over 150 million children under five years of age are stunted, over 50 million are wasted, and approximately 17 million are seriously wasted. Nearly half of children under five in the world with stunting and two-thirds of all wasted children under five in the world lives in Asian countries. Despite the decline in malnutrition among the developing countries, still about 71 million malnourished children residing in India, Nigeria and Pakistan.[4, 5]

Pakistan is amongst the top ten countries in the world where over half of the population under five is stunted, wasted, or both. According to the national nutritional survey 2018, malnutrition is on the rise in Pakistan with nearly one in three children (28.9%) being underweight, four out of ten being stunted (40.2%), and 17.7% suffering from wasting.[6]

Early nutritional deficiencies are linked to poor reproductive outcomes, work capacity, intellectual performance, and overall health in adulthood and

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adolescence in the long run.[2,7] As per UNICEF the major factors of childhood under nutrition can be grouped into 3 major underlying factors as; domestic food insecurity, unhealthy domestic environment and inadequate care, and absence of healthcare services.[6] These sequentially are influenced by employment, poverty, income, dwelling, remittances and assets which are also affected by political and socio-economic factors. Keeping in view such findings regarding factors responsible for malnutrition in children under five years, this study has been conducted to determine the association between socio-demographic and child related factors with malnutrition (under-nutrition) among children having age less than five years in Hyderabad, Sindh.

MATERIALS AND METHODS

Cross-Sectional study was conducted at the Pediatric department, Liaquat University Hospital Jamshoro from August 2020 to Feb 2021. Children visited the pediatric out-patient and/or admitted in pediatric unit during the study duration, aged 6–59 months, regardless of gender, anthropometric measurements not appropriate for their age and whose guardians/parents given permission of participation were included. Whereas, with associated illnesses like congenital abnormalities (like congenital heart diseases), renal failure, metabolic disorders and endocrine disorder and their parents unwilling to take part in the study were excluded.

Children were selected through non-random purposive sampling technique. Sample size of 384 was calculated using standard formula $n=z^2p\ (1–p)/d^2$, where 'z' representing the confidence level of 95% (keeping the value of 1.96), 'p' is the estimated prevalence of malnutrition in under-five children in the Sindh which is 51.6% based on available information[2] and 'd' representing 5% (0.05) significance level.

After getting ethical approval from the Ethical Review Committee (ERC) LUMHS, and informed consent from the parent or guardian of the participants, data was collected using a semi-structured written questionnaire. Children information regarding socio-demographic details, economic condition, parent's information, history of documented diseases, breast feeding status, initiation of weaning time, healthcare seeking behavior etc. were inquired. A digital scale (automated weighing scale) with 100 gram (0.1 kg) gradients was used to determine the child's weight. Height of children (< 2 years) was computed using a length board (infantometer, Baby Weight Machine Unique YRBB-20, China) while height of children (> 2years) measured using a stadiometer up to 0.1 cm (MS Scale Bathroom Camry BR9011). Anthro-plus calculator was used to evaluate the nutritional status of participating children.

Collected information was exported to SPSS version 23.0 and analyzed. Multivariate logistic regression analysis model was applied. Significance level was set as $p<0.05$.

RESULTS

Total 384 children participated in the study. The overall mean age of participants was 24.4±11.4 months. Majority 98(25.5%) of children belongs to age 36-47 months. Mothers of 219(57.0%) participants were had no formal education whereas, amongst the fathers of participants, 117 (30.4%) don't have any formal education. Total 124 (32.3%) had family income of 21 to 30 thousand rupees /month, most 180(47.0%) lives in a joint family.

Figure 1 is demonstrating the under-nutrition status of study participants. Most of the participants had stunted growth. (Figure 1).

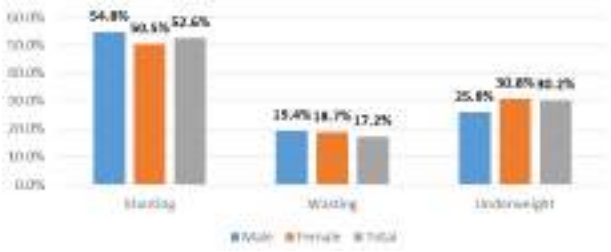

Figure No.1: Gender-wise distribution of under-nutrition details among study participants

Table I is showing the association between child characteristics and under-nutrition among the study participants. Statistically significant association ($p<0.05$) between child's age, birth order, history of measles and diarrhea with the nutritional status.

Parental factors like maternal (mother) education, paternal education, paternal (father) occupation, family type, family income per month and house type showed a statistically significant relation ($p<0.05$) with the under-nutrition. (Table 2).

Total duration of breastfeeding, time of weaning initiation, hand washing practice prior to meals, vaccination status and health seeking behavior had a statistically significant association ($p<0.05$) with under-nutrition. (Table 3).

Table No.1: Multiple logistic regression model for association between Child characteristics and under-nutrition among study participants

	Stunting		Wasted		Under-weight	
	O.R. (C.I. 95%)	P value	O.R. (C.I. 95%)	P value	O.R. (C.I. 95%)	P value
Gender						
Boy	Reference					
Girl	1.87 (1.62-1.95)	<0.001	1.16 (0.70-1.70)	0.360	1.44 (0.92-2.09)	0.254

Age						
6-11	Reference					
12-23	2.44 (2.20-2.85)	<0.001	1.54 (1.27-1.66)	<0.001	1.31 (1.23-2.01)	0.033
24-35	2.08 (1.51-3.41)	0.001	1.32 (1.07-2.11)	0.001	1.19 (1.13-2.30)	0.032
36-47	1.31 (1.20-1.68)	<0.001	0.51 (0.29-0.79)	<0.001	0.39 (0.25-0.81)	0.015
48-59	0.82 (0.63-0.95)	<0.001	0.61 (0.42-0.78)	<0.001	0.49 (0.33-0.79)	0.012
Child's Birth Order						
1st	Reference					
2nd	1.59 (1.14-2.56)	<0.01	1.31 (1.18-2.17)	0.001	1.28 (1.16-1.52)	<0.001
3rd	1.51 (1.25-2.40)	<0.001	1.17 (1.12-2.04)	0.001	1.44 (1.22-3.32)	<0.001
4th & above	2.5 (1.40-3.70)	0.030	2.27 (1.27-4.05)	0.001	3.08 (2.11-8.5)	<0.001
Fever in last 15 days						
Yes	Reference					
No	0.60 (0.15-1.36)	0.883	0.78 (0.32-0.53)	0.594	0.62 (0.15-1.36)	0.883
Measles in last 15 days						
Yes	Reference					
No	0.69 (0.44-0.87)	0.030	0.62 (0.40-0.96)	0.033	0.55 (0.44-0.69)	0.001
Diarrhea in last 15 days						
Yes	Reference					
No	0.65 (0.49-0.86)	0.001	0.77 (0.51-0.89)	0.001	0.60 (0.46-0.78)	0.001
Respiratory infection in last 15 days						
Yes	Reference					
No	0.98 (0.82-1.19)	0.883	0.99 (0.82-1.19)	0.872	0.94 (0.74-1.19)	0.618

Table No.2: Multiple logistic regression model for association between socio-demographic and parents factors with under-nutrition among study participants

	Stunting		**Wasted**		**Under-weight**	
	O.R. (C.I. 95%)	P value	O.R. (C.I. 95%)	P value	O.R. (C.I. 95%)	P value
Maternal education						
Bachelors/ Diploma	Reference					
High school	1.43 (1.12-1.83)	0.002	0.87 (0.5-1.95)	<0.001	0.85 (0.41-0.96)	<0.001
Primary	1.78 (1.42-1.97)	<0.001	0.45 (0.15-0.92)	<0.001	0.56 (0.34-1.85)	<0.001
Illiterate	1.86 (1.37-2.05)	<0.001	0.38 (0.22-0.68)	<0.001	0.73 (0.36-1.35)	<0.001
Paternal (Father) Education						
Bachelors/ Diploma	Reference					
High school	1.32 (1.08-1.55)	0.017	0.60 (0.20-0.95)	0.001	0.87 (0.36-0.91)	<0.001
Primary	1.40 (1.03-1.60)	0.032	0.71 (0.52-0.98)	0.001	0.51 (0.34-1.85)	<0.001
Illiterate	1.28 (0.86-1.46)	0.056	0.29 (0.12-0.69)	0.001	0.69 (0.36-1.05)	<0.001
Father Occupation						
Employed	Reference					
Unemployed	0.57 (0.22-0.89)	<0.001	0.54 (0.07-0.95)	0.004	0.49 (0.12-0.80)	<0.001
Family Type						
Joint	Reference					
Nuclear	2.03 (1.28-3.24)	0.005	1.36 (1.22-2.02)	0.001	1.70 (1.29-2.55)	0.002
Family Income / Month (PKR)						
≥ 41000	Reference					
31000-40000	1.90 (1.01-3.80)	0.040	1.19 (1.11-2.18)	0.033	0.50 (0.24-0.82)	0.042
21000-30,000	0.82 (0.42-0.96)	0.027	0.74 (0.40-0.87)	0.036	0.080 (0.40-0.95)	0.011
≤ 20,000	1.64 (1.30-2.14)	<0.001	0.59 (0.25-0.71)	0.002	0.30 (0.08-0.72)	0.017
House Type						
Cemented	Reference					
Semi Kaccha	0.72 (0.60-0.85)	0.021	0.76 (0.66-0.87)	0.001	0.85 (0.74-0.97)	0.017
Kaccha	0.57 (0.48-0.77)	0.028	0.60 (0.52-0.89)	0.001	0.66 (0.57-0.76)	0.001

Table No.3: Association between child caring practices and under-nutrition among the study participants

	Stunting		Wasted		Under-weight	
	O.R. (C.I. 95%)	P value	O.R. (C.I. 95%)	P value	O.R. (C.I. 95%)	P value
Initiation of Breastfeeding						
Immediately	Reference					
After an hour	1.12 (0.73-1.73)	0.467	1.60 (0.91-2.34)	0.312	1.64 (0.85-2.68)	0.825
Duration of Breastfeeding						
< 12 months	Reference					
> 12 months	0.13 (0.07-0.23)	<0.001	0.27 (0.12-0.38)	0.004	0.69 (0.54-0.88)	<0.001
Weaning Starting						
> 6 months	Reference					
≤ 6 months	1.88 (1.54-2.74)	<0.001	1.45 (1.28-1.72)	<0.001	1.16 (1.11-1.65)	<0.001
Hand Washing Prior to Meal						
Yes	Reference					
No	1.39 (1.25-1.75)	0.026	1.30 (1.14-1.49)	0.001	1.20 (1.15-1.43)	0.039
Hand Washing after Using Toilet						
Yes	Reference					
No	3.72 (0.56-5.66)	0.322	3.80 (0.74-3.75)	0.206	5.76 (0.46-9.58)	0.125
Vaccination Status						
Yes	Reference					
No	4.36 (2.32-8.71)	0.012	4.16 (2.18-7.93)	0.026	4.45 (2.77-7.14)	<0.001
Healthcare Seeking						
Yes	Reference					
No	6.8 (3.90-11.87)	<0.001	4.62 (2.83-7.53)	0.006	5.46 (3.25-9.09)	0.001

DISCUSSION

The prevalence of stunting in our study area was 52.6%, which is of Public health significance is very high "Very High" public health significance. While there is an excessive amount of wasting (17.2%) and underweight (30.2%) in children in this study. The significant prevalence of stunting indicates that these children are undernourished on a long-term basis. This might be brought on by mothers' low socioeconomic and educational standing. Findings of under-nutrition in our study is consistent with that of reported in Nutritional survey of Pakistan 2018.[8] Moreover, our findings are consistent with the studies by Asfaw et al. and Ali A. et. al., these studies have pointed the higher prevalence of under-nutrition among their study participants as mentioned in the present study.[9,5] While findings reported by Ahmada H, et al. related to prevalence of under-nutrition are not consistent with our study.[10]

The pattern of distribution of stunted growth and wasting among male and female children remain same in the present study. While male participating children were more underweight than their counterparts. These findings are consistent with the findings reported in Pakistan's national nutritional survey 2018. The pattern of gender wise distribution of under-nutrition is also in line with Fantahun W, et al and Alemayehu M, et al even though the disparity in nutritional status was similar to that found in a study done in Sindh, Pakistan by Khan GM. et. al.[11,12,3] Significant relations between maternal education and under-nutrition among children have reported by several studies. Our study findings related to maternal education, maternal employment status, father education, monthly family income and resident type are consistent with different studies conducted worldwide.[3, 11, 13-15]

Studies stated that under-nutrition among children born later in order was higher compared with those born earlier.[3, 16, 17] This may be due to the fact that maternal stores get depleted owing to multiple pregnancies resulting in lack of meeting the child nutritional requirements. Duration of breastfeeding, initiation of weaning and vaccination status had a significant association in this study. These findings are consistent with several studies reported the significant association of under-nutrition with these factors.[3, 9, 18, 19] When compared to children who started weaning after six months, children who started weaning before six months have significantly higher odds of being undernourished. The majority of kids were breastfed, which, by itself, cannot satisfy their nutritional needs, especially after six months. The absence of supplemental feeding may contribute to the explanation of why under-nutrition in children grew with age. Due to poverty and lack of access to a diet rich in nutrients,

the majority of children in Pakistan's rural areas are given wheat bread, which cannot by itself meet their nutritional needs.

CONCLUSION

The study concluded that high prevalence under-nutrition (stunting, wasting and underweight) among children 6-59 years in Hyderabad, Sindh. Different factors associated with the nutritional status of children include child age, birth order, diarrheal and measles morbidity, parental education, father occupation, family income, house type, health seeking behavior and vaccination.

Author's Contribution:

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Revisiting Critically:	Zoheb Rafique Memon, Munnawar Haque
Final Approval of version:	Munnawar Haque

Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Diagnostic Accuracy of Alvarado and Appendicitis Inflammatory Response Score in the Diagnosis of Acute Appendicitis

Sohail Aziz Paracha[1], Imtiaz Ahmed Khattak[2], Waleed Mabood[1], Muhammad Kabir Khan Afridi[4], Khurram Saidal[2] and Mussrat Jabeen[3]

ABSTRACT

Objective: To evaluate diagnostic accuracy of Alvarado score (AS) and Appendicitis Inflammatory Response (AIR) score in the diagnosis of acute appendicitis (AA) in our setup undergoing emergency appendectomy, keeping histopathological findings as gold standard.

Study Design: Cross sectional study.

Place and Duration of Study: This study was conducted at the surgical department DHQ Teaching Hospital and Sarhad Surgical Hospital, Kohat, Pakistan from January 1, 2022, to June 30, 2022.

Materials and Methods: Total of 204 consecutive suspected cases of AA were included in the study. Alvarado and AIR scores were prospectively calculated and postoperative histopathological confirmation report was obtained for each case. The validity of scoring systems was assessed in terms of sensitivity, specificity, positive predictive value, diagnostic accuracy and area under the receiver operating curve (AUC).

Results: The study comprised of 204 patients having mean age of 27.08±11.30 years with 111 (54.41%) males and 93 (45.59%) females. Confirmed cases of AA were seen in 114/119 and 55/85 patients at AS >7 and <7. AIR score >8 and <8 revealed confirmation of AA in 130/134 and 57/68 patients respectively. AS showed sensitivity, specificity, positive predictive value of 64.70%, 88.23%, 96.49% and accuracy of 68.62% while for AIR it was 70.58, 94.11%, 98.36% and 74.50% respectively. Furthermore, AUC for AIR score was found to be better (0.70) than Alvarado score (0.64).

Conclusion: Alvarado and AIR scores have fair diagnostic accuracy of approximately 72%. Application of Alvarado and AIR scores for the diagnosis of AA can decrease avoidable radiological and surgical interventions.

Key Words: Acute appendicitis; Alvarado score; AIR score; Histopathology; Appendectomy; Diagnostic accuracy

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INTRODUCTION

Acute appendicitis (AA) is one of the commonest abdominal surgical emergencies over all age groups with a lifetime risk of 7-8%.(1) It affects 7%-10% of the world population.(2) It is more frequent in Asian countries including Pakistan with estimated incidence of 21%.(3)

Despite so much frequent occurrence and the technological advancements in diagnostic techniques, the diagnosis of AA still remains uncertain in many cases especially in young women and children leading to undue delay in diagnosis resulting in complications. Although AA is mainly a clinical diagnosis depending upon careful clinical history and physical examination but many clinical conditions mimic AA as well as AA has atypical presentation in 50% of the cases.(4) So a quick and timely diagnosis is necessary in making decision of management plan and to prevent unnecessary negative appendectomies resulting in higher finances and morbidity and mortality. Hence, it is beyond question that a quick and easy modality is inevitable to diagnose AA in a resource limited clinical settings which can be of great help to practising surgeons.

Various scoring systems have evolved over time to assist the clinical diagnosis of AA in suspected cases but only a few have proven acceptable. The diagnostic accuracy of AA has enhanced only slightly in the last few years. The characteristic triad of a history, clinical examination and leucocytosis has a diagnostic accuracy rate < 80%, and whilst radiological modalities like Abdominal scan and computed tomography if included, accuracy does not even reach 90%. but CT scan has

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some drawbacks and ultrasound is operator dependent. The Alvarado scoring (AS) system ie famous and frequently used due to its easy applicability and very good sensitivity and specificity.[2] But AS misses many cases – depending on the severity score and over predicting some cases particularly in women.[5] The Appendicitis Inflammatory Response (AIR) scoring reported in 2008 has been regarded as a better diagnostic tool by many researchers particularly in the West [2, 5, 6] as it has better specificity and positive predictive value than AS because it incorporates C-Reactive Protein, a well-proven important biomarker, as a variable in addition to taking into consideration objective patient's symptoms.

Alvarado score is commonly used in Pakistan and more statistics are available on it while AIR score is less commonly used clinically; so there is a need to measure the diagnostic accuracy of both diagnostic tools simultaneously in same patients to determine the better scoring modality in our settings having completely different ethnic background and diet. Furthermore, differences have been observed in accuracy when the mentioned scores are applied to varied populations.

MATERIALS AND METHODS

This cross sectional study was conducted at Surgery Department, DHQ Teaching Hospital KDA Kohat and Sarhad surgical Hospital, a private surgical Hospital at Kohat, Pakistan from January 1, 2022, to June 30, 2022. The study was priorly approved from the ethical board and research committee of the hospital and informed consent for participation in the study was obtained priorly. Sample size calculation was done using standardized formula for sample size assessment for diagnostic test studies.[7] Total of 204 patients of any age and either gender presenting with sudden-onset and non-traumatic right lower quadrant abdominal pain, suspected to be having AA (inflammation of appendix of less than 4 days duration) were collected by consecutive sampling technique. All those cases with appendicular lump, pregnant ladies, patients with previous abdominal surgery or known cases of abdominal malignancy and patients who showed unwillingness for surgical intervention were excluded from the study.

Detailed physical examination was done and laboratory investigations including blood complete count, urine routine examination and C-reactive protein was carried out in all admitted patients. Abdominopelvic ultrasonography was conducted in some selected cases especially in females to rule out differential diagnosis. Alvarado score (AS) of 7 and AIR score of 8 were taken as high probability for acute appendicitis as per available literature.[8, 9] Preoperatively, Alvarado and AIR score of each patient was recorded. AS of >7 and AIR score of >8 was indicative of acute appendicitis but AS <7 and AIR score <8 meant normal appendix but the decision for surgical intervention was only based upon clinical suspicion. All the cases underwent open emergency appendectomy under general anaesthesia after taking informed consent. Intra-operative findings were noted and routine post-operative care was given to all the patients. Uncomplicated appendicitis means all those patients having no evidence of perforation or abscess formation, and in which the inflammation is typically limited to the appendix while complicated appendicitis includes all those cases having perforation of the appendix, abscess formation or empyema. Normal appendix intraoperatively means appendix which looks normal with naked eye appearance on operation. Each resected specimen of appendix was referred to department of Pathology for histopathology. Acute appendicitis was established histopathologically when there was exudation in all the layers of appendix with infiltration of neutrophils granulocytes into the muscularis propria layer. Alvarado and AIR scores were correlated with resected appendicular histopathological findings. The outcome was classified as true positive (TP), true negative (TN), false positive (FP), false negative (FN) and the paired measures of diagnostic accuracy i.e., the sensitivity (Sen), specificity (Spe), positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy (DA) rate and AUR were calculated. The area under the receiver operating characteristic (ROC) curves was used to examine the performance characteristics of the scoring systems individually.

Data was prospectively collected on a well-structured proforma and statistical analysis was conducted through SPSS version 25. Frequency and percentage were computed for qualitative variables like gender. Mean±SD was used for quantitative variables like age. The data were labelled through the histopathologically confirmed diagnosis and paired measures for the Alvarado and AIR scores were calculated as per standard formulae for sensitivity, specificity, positive predictive value and negative predictive value. The two by two table designs were drawn to determine diagnostic accuracy.

RESULTS

Out of 204 patients, 111(54.41%) were males and 93 (45.59%) females with female to male ratio of 1:1.19. The most common (50.98%) observed affected age group was 21-40 years. The age and sex distribution of the patients has been depicted in Table I. There were 114 patients having AS of >7 while 90 patients had score of <7 while 122 patients showed AIR score of >8 and 82 patients were observed to have score <8.

The AIR score ranged from 6-11 with mean of 8.82±2.93 and AS ranged from 5 to 9 with a mean of 7.53±2.52 respectively. Out of 204 patients, 191 (93.62%) cases were diagnosed intraoperatively and

acute appendicitis was confirmed histopathologically in 110 (96.49%) and 120 (98.36%) patients at Alvarado >7 and AIR >8 scores respectively. Table-2 & 3 represent the values of test and disease positive cases with sensitivity, specificity, positive predictive value, negative predictive value and accuracy of Alvarado and AIR scores for both the risk groups. Overall the diagnostic accuracy of AS and AIR scoring systems in diagnosis of acute appendicitis was found to be 71.56% at the maximum cutoff values. The commest intraoperative finding was of uncomplicated appendicitis 147 (72.05%) and overall negative appendectomy rate (NAR) was found to be 5.13%. The predictive validity of AS as assessed by area under the ROC curve was 0.64 as compared to 0.70 for AIR score with cutoff values of 7 and 8 respectively (Figure 1).

Table No.1: Age and sex distribution with type of appendicitis, observed in suspected cases of acute appendicitis (n=204)

Age group (years)	Total (n=204)		Males (n=111)		Females(n=93)		Type of appendicitis		
	Frequency	%age	Frequency	%age	Frequency	%age	Uncomplicated	Complicated	Normal
<20	84	41.17	46	41.44	38	40.86	65	15	4
2 -40	104	50.98	56	50.45	48	51.61	74	22	8
41-60	12	5.88	6	5.40	5	5.37	6	5	1
>61	4	1.96	3	2.70	2	2.15	2	2	0

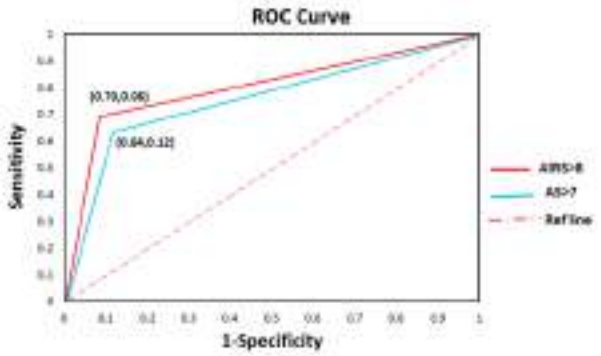

Figure No.1: ROC of the AIR & Alvarado scores at their maximum cutoff values in the study population

Table No.2: Risk score of Alvarado and histopathology findings in study population when cutoff is 7 (n=204)

	Histo-pathology +	Histo-pathology -	
AS>7	110 (TP)	4 (FP)	114
AS<7	60 (FN)	30 (TN)	90
	170	34	204

AS >7=Sen: 64.70%, Spe: 88.23%, PPV: 96.49%, NPV: 33.33%, DA: 68.62%, NAR: 3.50%

Table No.3: Risk score of AIR and histopathology findings in study population when cutoff value is 8 (n=204)

	Histopathology +	Histopathology -	
AIR>8	120 (TP)	2 (FP)	122
AIR<8	50 (FN)	32 (TN)	82
	170	34	204

AIR>8=Sen: 70.58%, Spe: 94.11%, PPV: 98.36%, NPV: 39.02, DA: 74.50%, NAR: 1.63%

DISCUSSION

The analysis of current study revealed better sensitivity and specificity of AIR score (70.58% & 94.11%) as compared to AS (64.70% and 88.23%) at high risk levels. Similarly, positive predictive values of AIR scores (98.36%) was observed as compared to AS (96.49%) at risk category. AIR and Alvarado scoring systems performed better at high-risk levels showing accuracy of 74.50% and 68.62% respectively. The negative appendectomy rate for AS and AR were found to be 1.63% and 3.50% respectively while AUC for AIR score was found to be better (0.70) than Alvarado score (0.64) at high probability levels. On the other hand low-medium risk categories of both Alvarado and AIR scoring systems (25.49% Vs. 31.37%) were quite unhelpful in estimating diagnosis of AA.

In our study out of 114 (55.88%) cases having Alvarado score of >7, 110 patients showed histopatological evidence of AA with PPV of 96.49% and specificity of 88.23% which is comparable to study conducted by other researchers across the globe.[9-11] Contrarily, some studies have reported lower PPV from 79-90% and specificity of 75-83%..[12, 13] Alvarado[14] recommended that patients with an AS of >7 should directly undergo surgery without any more workup. As far as AIR score of >8 is concerned out of 122 patients, 120 showed histopatological evidence of AA with PPV of 98.36% and specificity of of 94.11% which is in consistent with studies conducted by other researchers worldwide.[4, 8, 11] NAR at Alvarado score >7 was observed to be 3.50% means 4 patients with >7 score had non-inflamed appendix which is in accordance with study conducted by other investigators.[9, 15] On the other hand some rearchers have shown higher NAR ranging from 11-20% at Alvarado score >7.[12, 13] Similarly NAR at AIR score >8 was observed to be 1.63% means two patients showed normal appendix hispathlogically which is in accordance with study conducted by Karki OB and Hazara NA.[4] Conversely our study cohort showed evidence of AA on histopathology in 60.97% and 66.66% cases with negative appendectomy in 30/90 and 32/ 82 patients at Alvarado score <7 and AIR score <8 respectively. Very low NAR observed in low-medium score groups in our study may be due to the fact that

many patients are referred from gyne department and primary health-care hospitals after taking initial treatment. Furthermore, such cases of low-medium probability group actually had AS score >5 and AIR score >6, which then proceeded for surgical intervention just on clinical suspicion. Increased number of histopathological diagnosis of acute appendicitis in these low risk groups reported in our series is comparable with that of Karki OB, Hazra NK.[4] Our study showed 66.66% evidence of AA on histopathology with NAR of 33.33% which may be due to the fact that this study was conducted in teaching hospital where cases were mostly referred from periphery after taking unwise use of antibiotics which may change the disease process and course.

The AIR score showed good performance than Alvarado Score because C-Reactive Protein shows a greater discriminative power as has been supported by 10 out of 11 comparative studies.[16, 17] Although some studies have recommended combined use of both the scoring systems to increase the diagnostic accuracy and good decision making to decrease negative appendectomies in suspected cases of AA.[2] Overall accuracy of both the scoring systems was found to be approximately 72% in our study which is comparable with studies conducted elsewhere.[4, 18]

The current study showed that the predictive validity of AS as measured by area under the ROC curve was 0.64 as compared to 0.70 for high probability scores showing a good statistical correlation between two scores. Karki OB and Hazra NK[4] in a study conducted on 217 Nepalese patients reported AUR for AS 0.58 and 0.70 for AIR respectively for high cutoff values while Pogorelic et al[19] found AUR of 0.74 for Alvarado score and Anderson et al[8] reported 0.83 for AIR at maximum cutoff values (>7 for AS and >8 for AIR).

The limitations of our study include relatively small sample size of the study population from a single centre and cross sectional nature of the study which could diminish the significance of the associations.. Further, multi-centric, prospective studies with larger sample size are recommended for precised and generalizable conclusions regarding diagnostic accuracy of AIR and Alvarido Score of acute appendicitis.

CONCLUSION

Alvarado and AIR scoring systems are useful tools as those are easy and simple to use in resource-limited settings. AIR showed relatively better specificity, positive predictive value and AUR than Alvarado scoring system. Furthermore, Alvarado and AIR scores revealed fair diagnostic accuracy of approximately 72%. Application of Alvarado and AIR scores for the diagnosis of AA can decrease avoidable radiological and surgical interventions.

Author's Contribution:

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Original Article

Efficacy of Intravenous Ibuprofen Versus Intravenous Ketorolac in the Management of Post-Operative Pain after Abdominal Surgeries

Aun Ali[1], Ammara Salam[1], Nadia Shahid[2], Jabbar Ahmed Qureshi[3], Mohammed Ahmed[1] and Yousuf Ali Lakdawala[1]

ABSTRACT

Objective: To identify the difference in post-operative pain control among patients undergoing abdominal surgeries with intravenous Ibuprofen compared to intravenous Ketorolac.

Study Design: Randomized controlled trial study

Place and Duration of Study: This study was conducted at the Pakistan Air Force Hospital, Base Faisal, Fazaia Ruth Pfau Medical College, Karachi from January 2021 to July 2021.

Materials and Methods: A total of 68 patients undergoing abdominal surgeries, were randomly assigned in 1:1 ratio to receive 800 mg IV-ibuprofen or 30 mg IV-ketorolac every 6 hours, first dose being given immediately after surgery. Visual analogue scores for pain at rest and pain at ambulation were assessed at 24 hours after surgery. Additional requirement of opioid analgesia (IV nalbuphine) was also recorded.

Results: There were 34 patients in Ibuprofen group and 34 patients in ketorolac group. The mean VAS pain score at rest for the Ibuprofen Group (Group A) was 2.7 whereas for the Ketorolac Group (Group B) it was 2.9 (p value 0.482). The mean VAS pain score at movement for the Ibuprofen Group (Group A) was 3.00 and for the Ketorolac Group (Group B) was 3.33 (p value 0.382).

Conclusion: It is concluded that Intravenous Ibuprofen can be used for post-operative analgesia with efficacy equal to ketorolac. This has also been recorded that administration of Ibuprofen leads to decreased opioid consumption for pain relief thus minimizing the risks associated with opioid analgesia. This is a single center study, we would need further studies to validate the findings.

Key Words: Postoperative pain, ibuprofen, ketorolac, visual analogue score, abdominal surgery

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INTRODUCTION

Postoperative pain can cause adverse effects on patients in terms of healing and recovery[1]. Abdominal surgeries usually have large incisions and can cause considerable amount of pain in the postoperative period. The pain does not only aggravate SIRS, but also causes delayed recovery, respiratory difficulties and increased length of hospital stay[2].

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A number of analgesics are used for this purpose, which include non-steroidal anti-inflammatory drugs, often supplemented by opioids. Although opioids provide good pain relief but can also cause reduced gut motility, increasing the risk of postoperative ileus[3]. This results in their limited use, leaving the choice of NSAIDs as a primary preference.

Ibuprofen is a commonly prescribed NSAID in the world which is also available over the counter. It is a non-selective inhibitor of COX1 and COX 2. Ibuprofen is used as an analgesic, anti-inflammatory and antipyretic and is easily tolerated. Although it serves as non-selective inhibitor, the ratio of COX-1 to COX-2 inhibition is 2.5:1, which ensures that there is decreased risk of gastrointestinal bleeding and other gastrointestinal issues and its analgesic and anti-inflammatory effects is via COX-2 inhibition[6]. The additional benefit of ibuprofen is its equal efficacy as analgesic compared to the narcotics without the adverse effects of opioid administration such as respiratory depression or reduced gut mobility.

Ibuprofen (IV) had been approved by FDA in 2009, adding to the analgesic options for healthcare providers[4]. Intravenous Ibuprofen is tolerated well by

the patients, including the older age group, with no need of dose adjustment in such groups[5]. In Pakistan it has been introduced for the first time, the local data about its efficacy and usage is missing. Therefore, the study aims to study the difference in postoperative pain control among patients receiving IV Ketorolac and IV Ibuprofen, undergoing abdominal surgeries.

MATERIALS AND METHODS

This is a randomized controlled trial, of patients undergoing abdominal surgery at Pakistan Air Force Hospital for a period of 6 months (Jan 2021-Jul 2021). Sample size was calculated using Taro Yamane method, and it came out to be 67. A total number of 68 patients were included in the study, divided into two groups; Group A (who received IV Ibuprofen) and Group B (who received IV Ketorolac) using envelope method.

Patients age 18 years and above, who underwent abdominal surgery (elective/emergency) were included in the study. Patients with history of immuno-compromised state (such as diabetes, immunosuppressive drugs), asthma, renal impairment, congestive heart failure, allergy to NSAIDs, peptic ulcer disease or upper GI bleeding, were excluded from the study. Informed consent was taken from patients meeting the inclusion criteria.

All patients underwent surgery by consultant surgeons at FRPMC. First dose of the analgesic was given in operating room (OR) immediately after surgery. IV ibuprofen (Group A) was given in the dose of 800 mg in 100 ml NS IV 8 hourly, IV Ketorolac (Group B) was given 30 mg IV 8 hourly. All patients were given IV acetaminophen 1 g every 8 hours. All patients were able to receive opioid (Inj. Nalbuphine 10 mg IV stat) if they experienced breakthrough pain. On first postoperative day, visual analogue scale (VAS) scores were recorded from the patients to assess pain at rest and pain at ambulation.

RESULTS

A total of 68 patients were included in the study, who fulfilled the inclusion criteria. Both Groups A and B contained equal number of patients (34 each). Out of these 68 patients, 45 (66.17%) patients were female and 23 (33.82%) patients were male. The mean age of the patients was 38.23. Patients that underwent Laparoscopic Cholecystectomy were 59, 28 patients in Group A while 31 patients were in Group B. A total of 9 patients underwent Laparoscopic Appendectomy, out of which 6 patients were in Group A and 3 patients were in Group B.

There were no statistically significant differences between the two groups in demographics and length of hospital stay. Patients of both groups were assessed for VAS pain scores at 24 hours post-surgery. The mean VAS pain score at rest for the Ibuprofen Group (Group A) was 2.7 whereas for the Ketorolac Group (Group B) was 2.9 (p value 0.482). The mean VAS pain score at movement for the Ibuprofen Group (Group A) was 3.00 and for the Ketorolac Group (Group B) was 3.33 (p value 0.382).

Table No.1: Comparison of Patients' Gender & their Age

Group	Gender		Age		
	Male	Female	Overall Patients	Male Patients	Female Patients
A	3 (30%)	7 (70%)	41.20 ± 8.23	48.00 ± 19.89	38.29 ± 8.40
B	3 (30%)	7 (70%)	47.10 ± 8.85	41.00 ± 15.97	49.71 ± 10.81

Table No.2: t-text

Group	Mean	Median	St. Deviation	P-Value
A	3.00	3.00	0.82	0.382
B	3.30	3.00	0.67	

By applying t-test, it is revealed that there is a very weak association between VAS (Movement) of both the groups ($p = 0.382$; $t = -0.896$); they are independent and there is no significant difference between tested variables. This also support when we find correlation among both variables that comes 0.000 and showing there is no linear relationship i.e. No correlation.

DISCUSSION

Ibuprofen is a non-selective cyclooxygenase inhibitor (COX) and is one of the most commonly prescribed NSAIDs. It has a potent role as analgesic and antipyretic, owing to its inhibitory mode of action on cyclooxygenases involved in prostaglandin synthesis[6]. The literature suggests that Ibuprofen can be used in patients for a short period of time with very few safety concerns[7,8]. Singla et al. conducted a placebo-controlled trial in 2010 where they found that Ibuprofen did not only contribute to reduce amount of post-operative pain but also led to less opioid consumption[7]. This not only enhances post-operative recovery but also leads to early discharge and less hospital stay. A similar study was conducted by Kroll et al. where they compared Ibuprofen along with Morphine to placebo along with Morphine among patients undergoing abdominal hysterectomy[9]. Their findings were reduction in use of morphine (19.5%) among the group receiving ibuprofen in addition to lower pain scores.

Our study differs from the abovementioned studies in the context that it does not compare ibuprofen with placebo, rather it compares ibuprofen with ketorolac. There have also been studies comparing Ibuprofen and Ketorolac for the post-operative pain control. Uribe et al have compared the efficacy of ibuprofen and ketorolac in terms of post-operative analgesia after arthroscopic knee surgery. They concluded that there were no significant differences in pain control, patient

satisfaction and adverse effects on the post-operative day between the two drug groups[10].

It has been suggested that Ibuprofen can be prescribed relatively safely for short term use in surgical patients for post-operative pain relief. Berges et al report that IV ibuprofen led to 52% reduction in pain score calculated by Visual Analogue Scale in comparison to the baseline pain level. Some of the adverse events demonstrated were pain at infusion site, nausea, anemia, flatulence and bradycardia[11]. Another study conducted by Chow et al evaluated the efficacy of ketorolac for the control of pain and opioid use postoperatively in laparoscopic urologic surgery. They had 55 patients enrolled in their study who were randomly allocated to receive IV ketorolac or placebo preoperatively. The pain scores were recorded as 2.2 and 4.5 for ketorolac and placebo, respectively. It was also observed that were no significant adverse effects with the administration of ketorolac pre-operatively and no cases of gastrointestinal bleeding or bleeding diatheses were recorded[12].

CONCLUSION

It is concluded that Intravenous Ibuprofen can be used for post-operative analgesia with efficacy equal to ketorolac. This has also been recorded that administration of Ibuprofen leads to decreased opioid consumption for pain relief thus minimizing the risks associated with opioid analgesia. This is a single center study, we would need further studies to validate the findings.

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Original Article

Risk Factors for Birth Asphyxia – an Experience from A Tertiary Care Setting

Risk Factors for Birth Asphyxia

Saima Bibi[1], Syed Yasir Hussain Gilani[2] and Sadia Bibi[3]

ABSTRACT

Objective: The aim of the study was to identify the risk factors associated with birth asphyxia in newborns.
Study Design: Descriptive cross-sectional study
Place and Duration of Study: This study was conducted at the Neonatology unit of Ayub Medical Teaching Institute over a period of one year from 1st March 2021 to 28th February 2022.
Materials and Methods: All neonates who were admitted with birth asphyxia were included in the study. Data was collected by nonprobability convenience sampling. Patient characteristics and maternal details were recorded on a predesigned proforma. Patients whose maternal history was not available were excluded from the study. Patients with major congenital malformations were also excluded from the study. Data was entered and analyzed using SPSS 26. Significance testing was done using Chi square test. P value of <0.05 was considered significant.
Results: A total of 110 patients were included in our study. These included 60(54.5%) male and 50(45.5%) female patients. Major antepartum risk factors included maternal anemia in 75(68.2%), un-booked status in 83(75.5%), PROM in 38(34.5%) and primiparity in 68(61.8%). Major intrapartum risk factors were prolong labour in 68(61.8%) and obstructed labour in 28(25.5%) patients. A total of 76(69.1%) patients were discharged and 34(30.9%) expired.
Conclusion: Maternal un-booked status, hypertension, prolong rupture of membranes, prolong labour and obstructed labour are associated with poor outcome in patients with birth asphyxia.
Key Words: Asphyxia, Risk Factors, Antepartum, Intrapartum

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INTRODUCTION

Birth asphyxia is considered as the inability to start and maintain respiration at the time of birth leading to impaired oxygenation in the lungs culminating in low oxygen and high carbon dioxide content.[1] American academy of pediatrics includes metabolic acidosis (pH<7) in cord blood, low APGAR Score 0-3 for more than 5 min, neurological involvement like convulsions, and multi organ dysfunction including kidney liver ,lungs, and heart, for labeling the patient as asphyxiated newborn.[2] The consequences of birth asphyxia includes damage to almost all vital organs like heart, liver, lungs and kidneys but the most devastating squeal are due to brain involvement leading to neurocognitive impairment and permanent disability.[3] Recent estimates suggest that an approximately 1 million newborn die every year due to birth asphyxia in the world. Around 2 million babies develop encephalopathy and about 1.2 million suffer from neurocognitive impairment.[4]

Medical research conducted worldwide has identified a number of potential contributors to birth asphyxia including maternal, intrapartum and neonatal risk factors.[5] These comprise antepartum factors including age and educational status of mother, maternal hypertension, primigravida mothers, malposition/ malpresentation, mode of delivery, labour duration etc during intrapartum period and prematurity, birth weight and fetal distress amongst the neonatal conditions.[6] Other risk factors implicated in the etiology of birth asphyxia include cord prolapse, shoulder dystocia, uterine rupture, placental abruption and two newer entities of obesity and previous caesarean section.[7] Literature suggests that the burden of neonatal deaths can be effectively reduced by using interventions in the intrapartum period including labour and delivery, hereby reducing mortality by up-to 79% during this phase.[8]

The present study was conducted to highlight the risk factors associated with birth asphyxia in our region. Identification of risk factors will serve as a basis for devising interventions aimed at ameliorating these risk factors and hence aiming to reduce morbidity and mortality associated with this condition.

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MATERIALS AND METHODS

This descriptive cross-sectional study was conducted in the Neonatology unit of Ayub Medical Teaching Institute over a period of one year from 1st March 2021 to 28th February 2022 after obtaining ethical approval. All neonates who were admitted with birth asphyxia were included in the study. Data was collected using nonprobability convenience sampling. Patient characteristics were recorded on a predesigned proforma. Details about maternal risk factors were obtained from either of the parents and recorded on the proforma. Patients whose maternal history was not available were excluded from the study. Patients with major congenital malformations were also excluded from the study. Data was entered and analyzed using SPSS 26. Significance testing was done using Chi square test. P value of <0.05 was considered significant.

RESULTS

A total of 110 patients were included in our study. These included 60(54.5%) male and 50(45.5%) female patients. Mean age of the participants was 1.39±.86 days. Mean weight of the participants was 2.80±0.56 kg. Mean age of the mothers was 25.00 ±5.60 years.

Table No. 1: Patient characteristics (n=110)

Mean age (days)	1.39±.86 days	
Mean weight(kg)	2.80±0.56 kg	
Mean maternal age (years)	25.00 ±5.60 years	
Gender	**Frequency**	**%age**
Male	60	54.5%
Female	50	45.5%
Gestational age		
Full term	100	90.9%
Pre term	10	9.1%
Mode of delivery		
SVD	63	57.3%
Assisted vaginal delivery	11	10%
Caesarean section	36	32.7%
Place of delivery		
Home	21	19.1%
Private clinic	8	7.3%
Hospital	81	73.6%
Outcome		
Discharge	76	69.1%
Expired	34	30.9%

A total of 100(90.9%) patients were born at full term while 10(9.1%) patients were preterm. A total of 81(73.6%) patients were delivered at hospital, 8(7.3%) at private clinic and 21(19.1%) at home. Major mode of delivery was spontaneous vaginal delivery in 63(57.3%), followed by Caesarean section in 36(32.7%) and assisted vaginal delivery in 11(10%) (Table:1) Major antepartum risk factors included maternal anemia in 75(68.2%), un-booked status in 83(75.5%), PROM in 38(34.5%) and primiparity in 68(61.8%). Major intrapartum risk factors were prolong labour in 68(61.8%) and obstructed labour in 28 (25.5%) patients**.**(Table:2) A total of 76(69.1%) patients were discharged and 34(30.9%) expired. Risk factors were assessed in relation to outcome. There was a statistically significant association of outcome to maternal un-booked status (p=0.002), Prolonged rupture of membranes PROM (p=0.002), maternal hypertension (p=0.03) prolong labour (p=0.001) and obstructed labour (p=0.01**)**(Table:3).

Table 2: Risk factors for birth asphyxia

Antepartum risk factors	**Frequency**	**%tage**
Young maternal age	19	17.3%
Advanced maternal age	12	10.9%
Maternal anemia	75	68.2%
Maternal PIH	25	22.7%
Gestational DM	13	11.8%
Multiple gestation	4	3.6%
Antepartum hemorrhage	5	4.5%
Primigravidity	68	61.8%
Unbooked status	83	75.5%
Maternal fever	23	20.9%
Maternal chronic illness	6	5.5%
Intrapartum risk factors		
PROM	38	34.5%
Prolong labour	68	61.8%
Obstructed labour	28	25.5%

Table No.3: **Risk factors in relation to outcome**

Risk factors		**Discharged**	**Expired**	**P value**
Maternal PIH	Yes	13	12	0.035
	No	63	22	
Booking status	Yes	25	2	0.002
	No	51	32	
Maternal anemia	Yes	49	26	0.212
	No	27	8	
APH	Yes	2	3	0.150
	No	74	31	
PROM	Yes	19	19	0.002
	No	57	15	
Maternal chronic illness	Yes	5	1	0.438
	No	71	33	
Prolong labor	Yes	39	29	0.001
	No	37	5	
Young age	Yes	14	5	0.634
	No	62	29	
Advanced age	Yes	7	s5	0.393
	No	69	29	
Gestational DM	Yes	10	3	0.515
	No	66	31	
Maternal fever	Yes	15	8	0.651
	No	61	26	
Obstructed labor	Yes	14	14	0.011
	No	62	20	

DISCUSSION

Majority of patients in our study were male. Similar results are reported from another study conducted at Hyderabad where 60% of the asphyxiated newborns were male. [9]A number of maternal risk factors was identified in our study in asphyxiated neonates. Parity had a significant association to birth asphyxia in our study. Majority of neonates were born to primigravida mothers. A study from Eithopia reports similar results where primiparous mothers were found to have a three fold higher risk of delivering neonates with birth asphyxia.[10]

Majority of asphyxiated neonates in our study were full term babies with good birth weight. This is in contrast to the results from other studies where low birth weight and preterm delivery were reported to be significantly associated with asphyxia [10,11]This difference may be attributed to different socioeconomic, cultural and genetic factors in different areas. However, another study from a rural area of Pakistan also documented a two fold higher risk of mortality due to birth asphyxia in good sized newborns.[12] Other risk factors identified as contributors to mortality in asphyxiated neonates in this study included maternal anemia, smelly vaginal discharge, prolong labour, maternal fever and maternal illiteracy.[12] Our study also yielded similar results.

A metanalysis from Eithopia identified antepartum hemorrhage, prolonged rupture of membranes, maternal anemia and hypertension, prolong labour, instrumental vaginal delivery, caesarean section and primiparity as potential risk factors for asphyxia in newborns.[13] Similar risk factors were also identified in our study.

Another study also documented significant association of birth asphyxia in primigravida, un-booked patients, home delivery and maternal fever. Mean age of mothers was about 24 years in this study.[14]. Both these findings are comparable to our study. Another study by Lee et al also identified maternal fever as a significant risk factor for birth asphyxia.[15] Another risk factor identified in the previous studies was the delivery conducted by untrained midwives in rural areas.[16] In our study, majority of the births took place in the hospital. However, these included those patients as well who underwent labour trials by the untrained birth attendants and were later referred to hospitals when complications developed.

CONCLUSION

Maternal un-booked status, hypertension, prolong rupture of membranes, prolong labour and obstructed labour are associated with poor outcome in patients with birth asphyxia. All these risk factors are amenable to be eliminated by instituting health awareness programs and implementing good antenatal and perinatal care.

Author's Contribution:

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Data Analysis:	Sadia Bibi, Syed Yasir Hussain Gilani
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Original Article

Hypothyroidism in Patients with Hepatitis C Infection Visiting a Tertiary Care Hospital

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ABSTRACT

Objective: The goal of this study is to assess the prevalence of hypothyroidism among hepatitis C patients, presenting to a tertiary care center.

Study Design: A cross-sectional study

Place and Duration of Study: This study was conducted at the Department of Medicine, Liaquat University of Medical & Health Sciences, Jamshoro between January 2022 and June 2022.

Materials and Methods: All patients who were aged between 18 and 65 years, irrespective of gender, who had been diagnosed with hepatitis C infection for more than 6 months and did not take any treatment for thyroid dysfunction were included in the study. Patients who were already diagnosed with thyroid diseases before the hepatitis C infection and were on treatment for thyroid dysfunction or underwent surgery or radiation were excluded from the study. All the information was collected on a prescribed proforma.

Results: A total of 151 patients were included in the study. A mean age of 45.7 ± 13.4 was observed, and a mean duration of 6.4 ± 3.8 months of hepatitis C infection was noted. A total of 37 out of 151 patients (24.5%) had hypothyroidism in our study. It was found that age between 18-40 years correlated substantially with a higher prevalence of hypothyroidism.

Conclusion: The study concluded that hypothyroidism was documented in a large number of patients presenting with hepatitis C infection.

Key Words: Hepatitis C Infection, Hypothyroidism, Thyroid Stimulating Hormone, Hyperthyroidism

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INTRODUCTION

Chronic hepatitis, hepatic cirrhosis progressing to hepatic failure, and hepatocellular cancer are almost always caused by the hepatitis C virus (HCV). Treatment for HCV infection often begins with interferon and continues with ribavirin. Some patients with HCV experience thyroid problems due to the virus itself, but prospective studies have shown that patients receiving interferon therapy may develop clinical thyroid disease, which may result in the discontinuation of therapy.

Interferon and ribavirin may trigger the production of different antibodies, which could be a possible cause of thyroid dysfunction. Early thyroid disease diagnosis and treatment are crucial to preventing problems [1-2].

HCV infection rates in Pakistan are 30%, with a 2.3% prevalence in children, a 5.2% prevalence in pregnant women, a 3.1% prevalence in army recruits, a 3.6% prevalence in blood donors, a 5.4% prevalence in healthcare workers, a 10.3% prevalence in those at high risk, a 12% prevalence in those with a provisional diagnosis of HCV infection, and a 54% prevalence in those with chronic HCV infection [3]. Thyroiditis, which can be classified as autoimmune or non-autoimmune is mostly caused by FN-α. 20-40% of patients have subclinical thyroiditis but only 5-10% show clinically evident thyroiditis.[4-5] Autoimmune thyroiditis, often known as Hashimoto's thyroiditis, is characterized by the presence of or increase in antithyroid antibodies, regardless of the presence or severity of hypothyroidism. Destructive thyroiditis as well as hypothyroidism [6] are symptoms of Non-autoimmune IIT. The therapeutic effectiveness of IFN- in the management of chronic hepatitis C is well established. In fact, between fifty percent and seventy percent of patients can be cured when IFN- and RBV are used in tandem [7]. However, IFN- therapy is not without its own risks, and discontinuing treatment could lead to complications and even death. [8] Thyroid dysfunction was shown to affect between 3 and 14% of individuals

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in research done by Ward et al. in 2001, [9] 8.2% of HCV-infected patients and 10.7% of those with thyroid dysfunction were given IFN- medications in 2004, according to a study by Bini et al. [10]

Chachar AZ et al, concluded that 18.8% of patients had thyroid dysfunction, while 6.59% had hypothyroidism and 23.4% had hyperthyroidism.[11] Another study reported the incidence of hypothyroidism as 26% in patients with positive HCV. [12]

One of the most remarkable therapeutic successes of IFN- has been in the management of chronic hepatitis C, in which the combination of IFN- as well as RBV has been shown to promote remission in as many as 50% of patients. [11] However, there are several potential side effects of IFN- treatment, some of which are so severe that they can lead to morbidity and the need to stop therapy.[12] It has been established that infection with the hepatitis C virus is associated with both localized and systemic autoimmune disorders. Thyroid problems have been linked to chronic viral hepatitis in a number of ways. The cornerstone treatment medication for HCV infection is pegylated interferon. [13]

Numerous studies conducted in different parts of the world have attempted to quantify the frequency of hypothyroidism among patients with hepatitis C, but adequate data on this issue is absent in Pakistan. It is imperative that patients be identified sooner and that early therapy be enhanced in order to prevent consequences. The results of this research would be useful in estimating how common hypothyroidism is among people with hepatitis C.

MATERIALS AND METHODS

The endocrinology division at Liaquat University of Medical & Health Sciences, Jamshoro, conducted a cross-sectional study between January 2022 and June 2022. The institutional review board gave their blessing to the study before it began. Participants were recruited in the study by using a non-random sampling technique. All patients who were aged between 18 and 65 years, irrespective of gender, who had been diagnosed with hepatitis C infection for more than 6 months and did not take any treatment for thyroid dysfunction were included in the study. Patients who were already diagnosed with thyroid diseases before the hepatitis C infection and were on treatment for thyroid dysfunction or underwent surgery or radiation were excluded from the study.

By using the W.H.O sample size calculator using the frequency of hypothyroidism of 26% in the HCV-positive patients, [12] margin of error (d) = 7%, and confidence level (C.I) = 95%, the estimated sample size of n = 151 patients was included. With a TSH over 4.0 mIU/l and a free T4 below 11.0 pmol/l, hypothyroidism was diagnosed [12]. A patient with positive serology of anti HCV antibodies which were confirmed by ELISA method and HCV RNA by PCR were labeled as having hepatitis C infection.

All patients who visited the outpatient Department of Gastroenterology and fulfilled the inclusion criteria were included in the study. After outlining the technique, hazards, and advantages of the study, informed permission was obtained. Initially, each patient was evaluated based on their clinical, hematological, biochemical, and serological characteristics. Biochemical (liver function test, renal function test) and hematological (blood counts) routine testing were performed with the help of automated methods. Third-generation commercial enzyme-linked immunosorbent assay testing for HCV antibodies was used for detection. Determination of the RNA load of HCV was performed. Free thyroxine (FT4), free triiodothyronine (FT3), and serum thyrotropin (TSH) were measured using ultrasensitive immunological chemiluminescent noncompetitive assay to assess thyroid function (Access 2, Beckman Coulter). All the procedure was performed by the researcher himself under the supervision of a consultant > 5 years of experience. All the information was collected on a prescribed proforma. Biases and confounders were controlled by strictly following the inclusion and exclusion criteria.

The data was imported into SPSS version 21.0 and analyzed appropriately. For quantitative factors such as age, duration of hepatitis C infection, FT3, FT4, and TSH; the standard deviation and median were determined. Gender, hypertension, diabetes mellitus, and hypothyroidism were all provided as frequencies and percentages. To examine the influence of age, gender, duration of hepatitis C infection, FT3, FT4, TSH, length of hepatitis C infection, hypertension, and diabetes mellitus on outcome variables, data was stratified by age, gender, and duration of hepatitis C infection. Following post-hoc stratification, Chi-Square was used with a two-sided P 0.05 as the statistical significance criterion. For graphical data display, bar graphs and pie charts were employed as needed.

RESULTS

There were a total of 151 patients in the research group. The average age was 45.7 13.4 years old and a mean duration of 6.4 ± 3.8 months of hepatitis C infection was noted. Mean levels of thyroid hormones are illustrated in Table 1. The majority of the patients were male and almost one-half of the patients had hypertension. A total of 37 out of 151 patients (24.5%) had hypothyroidism in our study.

Stratification of age group (18-40) & >40, gender (male/female), FT3, FT4, TSH, hypertension and diabetes mellitus were done with respect to hypothyroidism in order to check significant differences as shown in Table 2. Hypothyroidism was shown to occur more often in people aged 18 to 40.

Hypothyroidism and diabetes mellitus were also strongly linked with hypertension, with a frequency of 23 (15.2%) and 21 (13.9%), respectively.

Table No.1: Distribution of patient characteristics

Characteristics	Mean ± SD
Age (years)	45.7 ± 13.4
Hepatitis C duration (months)	6.4 ± 3.8
FT3 (pg/ml)	2.65 ± 0.91
FT4 (ng/ml)	0.81 ± 0.19
TSH (uIU/ml)	2.37 ± 1.3
Gender	N (%)
Male	89 (58.9%)
Female	62 (41.1%)
Hypertension	70 (46.4%)
Diabetes mellitus	52 (34.4%)
Hypothyroidism	37 (24.5%)

Table No.2: Stratification of patient characteristics with respect to hypothyroidism

Charac-teristic	Hypothyroidism		P-value
	Yes	No	
Age			
18-40 years	20 (13.2%)	26 (17.2%)	<0.001
>40 years	17 (11.3%)	88 (58.3%)	
Gender			
Male	25 (16.6%)	64 (42.4%)	0.22
Female	12 (7.9%)	50 (33.1%)	
Hepatitis C duration			
6-8 months	28 (18.5%)	94 (62.3%)	0.363
>8 months	9 (6.0%)	20 (13.2%)	
FT3			
0.76-2 pg/ml	18 (11.9%)	44 (29.1%)	0.28
>2 pg/ml	19 (12.6%)	70 (46.4%)	
FT4			
0.77-1 ng/dl	26 (17.2%)	81 (53.6%)	0.927
>1 ng/dl	11 (7.3%)	33 (21.9%)	
TSH			
0.2-2 ulU/ml	24 (15.9%)	69 (45.7%)	0.637
> 2 ulU/ml	13 (8.6%)	45 (29.8%)	
Hypertension			
Yes	23 (15.2%)	47 (31.1%)	0.027
No	14 (9.3%)	67 (44.4%)	
Diabetes Mellitus			
Yes	21 (13.9%)	31 (20.5%)	0.001
No	16 (10.6%)	83 (55.0%)	

DISCUSSION

Hepatitis C has an extremely high prevalence in Pakistan, second only to Egypt. Right now, HCV infection affects roughly 10 million persons in Pakistan. [14] Many people who have had HCV infection have been treated with interferon injections. Several regional studies, [15–17] have reported on the occurrence of thyroid dysfunction with hepatitis C patients after interferon treatment, but only a few have assessed the prevalence of this issue before beginning treatment.[17,18] Twenty percent of untreated HCV patients in the area carried TPO-Ab, making them at increased risk for thyroid problems during and after interferon therapy.[19]

The mean lifespan of our patients was 43.712.4 years, which is in line with the findings of Vezali et al.[20] as well as Yan et al.[22] Whereas 89 (58.9%) of our patients were male and 62 (41.1%) were female, whereas Vezali et al[20] comprised 33 (54.1%) male participants and 28 (45.9%) female participants. The average TSH levels of the participants was 2.371.3 mIU/L, while the average TSH level in the study by Vezali et al.,[20] was 1.620.92 mIU/L. Therefore, it is analogous to our research. In our sample, there were 37 cases with hypothyroidism, or 24.5%. According to Vezali et al[20], 18% of people have hypothyroidism. Research by Yan et al[21] found that 6.4% of the population has hypothyroidism. Twelve out of 138 patients (8.7%) were found to have hypothyroidism, as reported by Foldes et al.[22] The findings of this study are consistent with those of all other investigations undertaken by various researchers.

The present study highlighted that a total of 37 out of 151 patients (24.5%) had hypothyroidism in our study. It was found that age between 18-40 years were significantly associated with higher frequency of hypothyroidism. Hypertension was also significantly associated with a higher frequency or hypothyroidism as well as diabetes mellitus with a frequency of 23 (15.2%) and 21 (13.9%), respectively.

Very little research has been done in Pakistan on the prevalence of hypothyroidism in infected individuals on interferon therapy. All patients with hepatitis C who are on pegylated interferon treatment for hypothyroidism can be tracked in this way, and medical staff can actively manage them to increase adherence.

CONCLUSION

It is to be concluded that hypothyroidism was documented in substantial numbers of newly diagnosed Hepatitis C patients. The study was applied only to a small sample of a single hospital, and the results may not reflect the scenario countrywide. It needs to be evaluated further in a larger group of patients at different hospitals in the country to generalize the findings of our study.

Author's Contribution:

Concept & Design of Study:	Ihsanullah Rajar
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Original Article

Two Sites Blood Cultures Compared to Standard Single Site Blood Culture in Diagnosis of Neonatal Sepsis

Haris Abdullah, Mimpal Singh, Shahida Nazir, Aneela Anjum and Liaqat Ali

ABSTRACT

Objective: To compare the yield of two sites blood cultures versus standard single site blood culture for the diagnosis of neonatal sepsis.

Study Design: Randomized Controlled Trial study

Place and Duration of Study: This study was conducted at the Neonatal Unit of Pediatric Medicine Unit-II, Mayo Hospital Lahore from March 1st, 2019 to August 31st, 2019.

Materials and Methods: 70% isopropyl alcohol were used to clean the skin upto 30 seconds to collect blood cultures, then cleaned again with 51-2% tincture of iodine and isopropyl alcohol. Blood samples of 11 mL were taken from each of the two peripheral veins and were inoculated into vials of BactT/Alert (Paed Plus). Observe cultures for 5 days before reporting a negative result. Single blood culture was taken of group-A and two blood culture was taken from group-B. In group- B, even single positive blood cultures were taken as significant and its yield was compared with group-A. Data were analyzed using SPSS v25.20. Data were stratified for age and gender to deal with effect modifiers. Post-stratification, Chi-Square was applied. A p-value ≤0.05 was considered significant.

Results: Total 150 neonates with suspected sepsis were enrolled for this study. Neonates were divided into two groups i.e. Group-A (Single site blood culture) and Group-B (Two site blood culture). In group-A, 54(72.40%) patients were male and 21(28.0%) were female. In group-B, 44 (58.7%) patients were male and 31 (41.3%) were female. In group-A, mean age was 14.94±7.69 days and 13.85±7.44 days in group-B. In single site blood culture group, 23 (30.7%) patients had positive yield and 42(56.0%) patients had positive yield two site blood culture group with a p-value of 0.002, which is statistically significant.

Conclusion: Two blood cultures collected synchronously from 2 places to increase pathogen detection rates as compare to conventional 1 culture blood.

Key Words: Neonatal Sepsis, Single Site Blood Culture, Two Site Blood Culture

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INTRODUCTION

Neonatal sepsis is the leading cause of neonatal deaths globally[1]. The incidence of neonatal sepsis in Pakistan is approximately 31.3/1000 live birth. Initial diagnosis and targeted treatment are key to reduce neonatal mortality from sepsis and the burden of antibiotic resistance development[2]. Blood cultures are still an important and Gold standard measure for the diagnosis of infection[3].

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Blood cultures in the neonatal period are contested in terms symptomatic accuracy due to intra-partum antibiotic, use previous antibiotic in referring hospitals, and growth of low microbial colonization number[4]. Different approaches were applied to increase the output of blood cultures. Such approaches involve the sort of large volumes of blood in vials, automatic systems to monitor the blood culture on regular basis and the adoption of numerous blood cultures, and the use of 2 or more than 2 blood cultures, maintaining a blood to broth ratio of 1:5 to 1:10 to avoid samples from indwelling catheters due to risk of contamination and use of repeat blood cultures.[5] In a study conducted by Tomar et al found that two blood cultures collected synchronously from 2 places to increase pathogen detection rates as compare to conventional 1 culture blood. They included 475 neonates with suspected sepsis out of which 185 patients had only the first positive culture (38.9%). When they added positives in the 2nd culture, the output improved up to 221 (46.5%).

Adding the 2nd culture improved culture output upto 36 (7.6%; 95% Cl 2.41 to 12.79; p=0.018)[6]. Wiswell et al were one of the first to document the two sites benefit of blood culture in the early examination of newborn sepsis. They collected two sample of blood cultures (aerobic and 1 anaerobic) from various places during the first week of life from 460 infants. Bacteremia was diagnosed in 8 cases, although contamination of the skin flora in 10 cases was confirmed.[7] Sarkar at el also conducted a study with two peripheral blood cultures in diagnosis of neonatal sepsis[8]. In a study, 73.1% were detected with first blood culture and 89.7% were detected with second blood culture.[9,10]

MATERIALS AND METHODS

This study was conducted at Neonatal Unit of Pediatric Medicine Unit-II, Mayo Hospital Lahore. Duration of Study: March 1, 2019 to August 31, 2019.

Study Design: Randomized Controlled Trial

Sampling Technique: Non-Probability Consecutive Sampling

Sample Size: Sample size of 150 (75 in each group) was calculated at 5% level of significance and 80% power of test and taking an expected percentage of yield in first culture as 73.1% and 89.7% in second culture.

Sample Selection:

Inclusion Criteria: All neonates of either gender having > Until the 28 days of life 130 weeks of gestation admitted to the unit. Patients with suspected neonatal sepsis as defined in operational definition.

Exclusion Criteria: Infected children who took antibiotics prior to sampling will be excluded.

Data Collection Procedure: After approval of the synopsis from the ethical review committee, informed consent was taken from the guardian of the child. All patients fulfilling the operational definition were recruited. Patients fulfilling definition were randomly divided in 2 groups, group-A and B by lottery method. 70% isopropyl alcohol were used to clean the skin up to 30 seconds to collect blood cultures, then cleaned again with 51-2% tincture of iodine and isopropyl alcohol. Blood samples of 11 mL were taken from each of the two peripheral veins and inoculated into BactT/ Alert vials (Paed Plus). Cultures observed for 5 days before reporting a negative result. Ingle blood culture was taken of group-A and two blood culture was taken from group-B. In group-B, even single positive blood cultures were taken as significant and its yield was compared with group-A.

Data Analysis Plan: Data were analyzed using SPSS v25.0. Mean and standard deviation were calculated for the quantitative variable like age. Frequencies and percentages were calculated for qualitative variables like gender and yield. Data were stratified for age and gender to deal with effect modifiers. Post-stratification, Chi-Square was applied. A p-value ≤0.05 was considered significant.

RESULTS

Total 150 neonates with suspected sepsis were enrolled for this study. Neonates were divided into two groups i.e. Group-A (Single site blood culture) and Group-B (Two site blood culture). In group-A, 54(72.40%) patients were male and 21 (28.0%) were female. In group-B, 44(58.7%) patients were male and 31(41.3%) were female. In group-A, mean age was 14.94±7.69 days and 13.85±7.44 days in group-B. In group-A, 40(53.3%) patients were in 0-14 days age group, while 35(46.7%) were in 15-28 days. In group-B, 41(54.7%) patients were in 0-14 days age group, while 34(45.3%) were in 15-28 days. In single site blood culture group, 23(30.7%) patients had positive yield and 42(56.0%) patients had positive yield two site blood culture group with a p-value of 0.002, which is statistically significant.

Table No.1: Comparison of gender distribution between groups

Gender	Groups		
	Single site blood culture	Two site blood culture	Total
Male	54	44	98
	72.0%	58.7%	65.3%
Female	21	31	52
	28.0%	41.3%	34.7%
Total	75	75	150
	100.0%	100.0%	100.0%

Table No.2: Comparison of age distribution between groups

Age Groups	Groups		
	Single site blood culture	Two site blood culture	Total
0-14 days	40	41	81
	53.3%	54.7%	54.0%
15-28 days	35	34	69
	46.7%	45.3%	46.0%
Total	75	75	150
	100.0%	100.0%	100.0%

DISCUSSION

In this study we have observed that taking two blood cultures increased the culture yield up to 25.3%. Primary morbidity was Comparable in children with one or two positive cultures, but greater than in children with two infertile cultures. In the past cultural-positive researches in infant have described isolation rates 25% to 60% [11-13]. Despite that some researches had indicated a decrease rate in the positivity of culture. This may be due to the lower amount of blood collected to

administrate the antibiotics before sampling[13-15]. Wiswell et al.[7] was one of the first to document the two sites benefit of blood culture in the earlier examination of newborn sepsis. They collected two sets of blood cultures (aerobic and 1 anaerobic) from various places during the first week of life from 460 inborn infants. Bacteremia was diagnosed in 8 cases, although contamination of the skin flora in 10 cases was confirmed. This study was retrospective that only included neonates up to 7th days of life.

Sarkar et al[8] in a prospective research blood cultures were collected from 2 different distal places within 15 to 30 minutes in 216 newborn with suspected sepsis. In their research 22 episodes of cultured sepsis occurred in 20 (9.2%) of 216 infants. All infants who have positive cultures developed the same organism with pattern susceptibility from 2 distal places. Blood cultures from both sites were negative for the remaining 196 neonates. They documented no benefit of two-site culture in detecting neonatal sepsis. The difference in the results of this study may be because of small size of sample and the involvement of only inborn neonates.

CONS and Candida spp. are often isolated organisms in newborns who have been admitted in neonatal intensive care center.[16] Since the particular microbes are element of the skin flora, those can be less contaminant in the blood culture process if the skin is not prepared well before the culture is performed[17-19].

Struthers, et al[20] was carried out a prospective study to differentiate pathogenic from contaminating CONS and reduce the use of antibiotics. After 48 hours of life, 100 pairs of cultures were taken from two percutaneous sites from 69 babies with suspected sepsis. They also considered one positive culture of CONS as contaminant and both positive cultures as infection. They differentiated between contaminating CONS in 5 new born grown in only one of the two cultures and pathogenic CONS in 16 neonates with both positive cultures. In contrast, a large proportion of the isolates in this study were reported as contaminants.

CONCLUSION

Two simultaneous blood cultures significantly improved the rate of where septic infants have a high rate of admissions. Two blood culture policy helps exclude contamination in units with high rates of these organisms.

Author's Contribution:

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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Short Term Outcomes of the Use of Antenatal Steroids in Preterm Infants

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ABSTRACT

Objective: To compare the short-term outcome of antenatal exposure to steroids in the case of planned and unplanned antenatal steroids.

Study Design: A **r**etrospective study

Place and Duration of Study: This study was conducted at the Neonatology Department of Recep Tayyip Erdogan Hospital Muzaffargarh between July 2016 till June 2021.

Materials and Methods: The cases of mothers who were at risk of preterm labor were given 12 mg dexamethasone 24 hours apart and then followed for the next seven days to determine the frequency of pregnancies delivered during the effective period of steroid, i.e., 24 hrs. after and within seven days of the last dose of steroid and then divided in two groups A and B. Group A included those who received Planned steroids and Group B included those who received Unplanned steroids. Data were compared between the two groups.

Results: Out of 201 preterm neonates, 140 (69.7%) were administered planned steroids. A total of 44 (21.89%) suffered from respiratory distress syndrome (RDS), 13 (6.47%) from retinopathy of prematurity, 11 (5.47%) from necrotizing enterocolitis, and 8 (3.98%) from pneumothorax. 8 (3.98%) preterm babies expired. Lower weight and gestational age were significantly associated with a higher rate of mortality ($p<0.0001$).

Conclusion: Patients with planned steroid administration suffered from significantly lower rates of neonatal complications than those with unplanned antenatal steroid administration.

Key Words: Antenatal Corticosteroids, Intraventricular Hemorrhage, Necrotizing Enterocolitis, Premature Birth, Respiratory Distress Syndrome, Retinopathy of Prematurity

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INTRODUCTION

Premature birth is a global anathema. [1] Its incidence is 7 to 12 % in developed countries,[2] while in Pakistan it is 21%. Death due to premature birth ranks second overall (28%).[1] Death from respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and retinopathy of prematurity (ROP), as well as premature birth's overall mortality rate, are all higher in premature infants. Complications of prematurity can be avoided by using antenatal steroids between 24 to 37 weeks of gestation.[3] In 1972, Sir Graham Collingwood Liggins with Ross Hawie became the first to legally sell anabolic steroids.[3-5]

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Antenatal steroids administration reduces admission to NICU, duration of hospital stay, financial burden, parental anxiety, separation of the newborn from the mother, and Increased risk of morbidity due to secondary infection acquired during the hospital stay. [4] Antenatal steroids reduce respiratory morbidity via different mechanisms. [1] By increasing the number and function of the Sodium channel in the apical membrane of the respiratory epithelium.[2] Increasing responsiveness to catecholamines and thyroid hormones. Steroids should be given to all women for whom a C-section is planned before 37 weeks.[3] Betamethasone and Dexamethasone are the most commonly used steroids.[6-9]

Antenatal corticosteroids have been shown to have deleterious impacts on the health, with no observable changes in the Doppler waveform sequences of fetoplacental arteries, but rather a decrease in i) fetal body, ii) fetal breathing movements, and iii) fetal heart rate variation. Multiple doses of corticosteroids given before delivery have been linked to decreased fetal growth inside the womb and lower birth weight babies. Neonatal sepsis can occur more quickly if the baby has been given steroids several times.[9-12]

Antenatal steroids are practiced and discussed worldwide a lot in the last decade or so, but up to our knowledge published data is insufficient. We have established gynae and neonatology units and have a

large amount of saved data regarding the use of antenatal steroids. We want to share and discuss our data and experience across the country and worldwide. The present study aimed to compare the short-term outcome of antenatal exposure to steroids in the case of planned and unplanned groups in terms of mortality and morbidity in neonates.

MATERIALS AND METHODS

A **r**etrospective study was conducted at the Neonatology department of Recep Tayyip Erdogan hospital Muzaffargarh and data of newborns who were delivered between 24 to 37 weeks of gestation from 1st July 2016 till 30th June 2021 were assessed after the ethical committee's exemption was approved.

Records were retrieved for all those neonates whose mothers had received antenatal steroids between 24 and 37 weeks of gestation were included in the study while all those neonates who were dysmorphic, hypoxic encephalopathy grade 3, complex congenital heart diseases, surgical anomalies were excluded.

The primary outcome of the study was the mortality rate and its association with the sociodemographic and antenatal parameters. The frequencies of respiratory distress syndrome (RDS), pneumothorax, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and retinopathy of prematurity were secondary outcomes.

Planned steroid was described as delivery conducted 24 hours after and within seven days of administration of 2nd dose of steroids.[15] Unplanned Steroid was described as delivery conducted less than 24 hours before 2nd dose and after seven days of the last dose of steroid.[15]

For the diagnosis of RDS, the patients must be a preterm neonate, suffer from respiratory difficulty within the first six hours of life, and lack lung expansion on skiagram; air bronchogram; reticulogranular pattern; ground-glass opacity.[8]

Pneumothorax was defined as air getting into the pleural space. [6] NEC was diagnosed upon radiographic proof of intestinal pneumatosis, pleural effusion, or subdiaphragmatic free air. [8]

IVH was diagnosed when preterm infants exhibited any three of the clinical criteria;

- Symptoms that appear within 0-72 hours of age
- Apneic episodes or convulsions
- Abrupt pallor or dropping hematocrit
- Profound hypotonia
- Confirmation of a flat or protruding fontanel via ultrasound, CT, or autopsy.[8]

Retinopathy of prematurity (ROP) preterm infants often develop a condition of the eye called retinopathy of prematurity, which is caused by the abnormal development of blood vessels in the retina. Infants born before the 31st week of pregnancy and weighing less than 2.75 pounds (1,250 grammes) are at increased risk for developing retinopathy of prematurity.[8]

Recep Tayyip Hospital, Muzaffargarh Neonatology Department comprises 25 neonatal beds delivering level III neonatal services to 10 and level II to 10 neonates. This institute uses HIMS for patient data. Our sample consisted of mothers whose newborns were admitted to the NICU and who used steroids throughout pregnancy, from 1st July 2016 till 30th June 2021. Those mothers who were at risk of preterm labor were given 12 mg dexamethasone 24 hours apart and then followed for the next seven days to determine the frequency of pregnancies delivered during the effective period of steroid, i.e., 24 hrs. after and within seven days of the last dose of steroid and then divided in two groups A and B.

Group A: Those who received Planned steroids

Group B: Those who received Unplanned steroids

We compared neonates of group A and B with respect to the short-term neonatal outcomes. We analyzed the data by using SPSS version 26. Frequencies and percentages of categorical variables (like gender, mortality) were reported. Mean (SD) or median (interquartile range) for numerical data (like weight, duration of respiratory support like oxygen, CPAP, Invasive ventilation). Chi-square test was applied to see the association of gender, mortality and other categorical variables with planned and unplanned steroids. A p-value less than 0.05 was considered statistically significant.

RESULTS

Table No.1: Demographic and Natal Characteristics of Study Subjects

Weight (grams)	2307.01 ± 465.7
Gestational age (weeks)	35.7 ± 2.3
Duration of hospital stay (days)	2.69 ± 3.8
Gender	
Female	95 (47.3%)
Male	106 (52.7%)
Mode of delivery	
Cesarean Section	153 (76.1%)
Spontaneous vaginal delivery (SVD)	48 (23.9%)
Planned steroid given	140 (69.7%)
Unplanned steroids given	54 (26.9%)
Duration of rupture of membrane >18 hrs	24 (11.9%)
Birth at own hospital	197 (98%)
Birth attended by trained personnel	198 (98.5%)
Stay at other hospital for >48 hours (out born)	161 (80.1%)

A total of 201 preterm neonates were assessed with a mean gestational age of 35.7 ± 2.3 months and a mean weight of 2307.01 ± 465.7 grams. 153 (76.1%) of the

mothers delivered via cesarean. 140 (69.7%) were administered planned steroids (Table 1).

In our study, 27 (13.4%) needed active resuscitation at the time of delivery and 47 (23.4%) required respiratory support during the hospital stay. 11 (5.47%) neonates were on invasive ventilation for 1-3 days, while 8 (3.98%) patients were ventilated for longer than three days. Moreover, cultures were positive for 25 (12.44%) patients, and 44 (21.89%) neonates were started on intravenous antibiotics.

A total of 44 (21.89%) suffered from respiratory distress syndrome (RDS), 13 (6.47%) from retinopathy of prematurity, 11 (5.47%) from necrotizing enterocolitis, and 8 (3.98%) from pneumothorax. 8 (3.98%) preterm babies expired. Neonates with a lower weight and a lower gestational age had significantly higher rates of RDS, intraventricular hemorrhage, necrotizing enterocolitis, and pneumothorax ($p<0.0001$). Neonates with longer duration of CPAP had significantly higher frequency of RDS, intraventricular hemorrhage, necrotizing enterocolitis, pneumothorax, and retinopathy of prematurity ($p<0.05$). RDS, intraventricular hemorrhage, necrotizing enterocolitis, pneumothorax, and retinopathy of prematurity were correlated with significantly longer duration of oxygen mask, invasive ventilation, and hospital stay ($p<0.05$).

Lower weight and gestational age were significantly associated with a higher rate of mortality ($p<0.0001$). Patients who expired had significantly longer duration of CPAP and invasive ventilation than those who survived. Gender and mode of delivery did not significantly correlate with mortality. Seven (87.5%) patients who had unplanned administration of steroids expired ($p<0.0001$) as illustrated in Table 2.

Table No.2: Association between subject characteristics and Mortality

	Mortality		
	No	**Yes**	**p-value**
Weight (grams)	2343.05 ± 428.8	1437.5 ± 504.09	<0.0001
Gestational age (weeks)	35.9 ± 2.048	30.88 ± 2.8	<0.0001
Duration of CPAP (days)	0.55 ± 1.266	1.5 ± 1.414	0.041
Duration of oxygen mask (days)	0.3 ± 0.656	0.75 ± 1.389	0.074
Duration of invasive ventilation (days)	0.19 ± 0.801	3.38 ± 1.061	<0.0001
Duration of hospital stay (in days)	2.56 ± 3.809	5.75 ± 2.915	0.021
Gender			0.378
Female	90 (46.6%)	5 (62.5%)	
Male	103 (53.4%)	3 (37.5%)	
Mode of delivery			0.106
Cesarean Section	145 (75.1%)	8 (100%)	
Spontaneous vaginal delivery (SVD)	48 (24.9%)	0 (0%)	
Planned steroid given	139 (72%)	1 (12.5%)	<0.0001
Unplanned steroid given	47 (24.4%)	7 (87.5%)	<0.0001

DISCUSSION

The present study revealed that patients with planned steroid administration suffered from significantly lower rates of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), pneumothorax, and mortality compared to those with unplanned antenatal steroid administration.

Our study was in accordance with published literature. Amorim et al., revealed the incidence of respiratory distress syndrome of 23%; lower in the steroid group compared to the placebo group. The rate of neonatal deaths was lower in the corticosteroid group (14% vs. 21%). In patients with severe preeclampsia between 26 and 34 weeks of gestation, antenatal corticosteroid therapy with betamethasone to accelerate fetal lung maturity is a safe and effective treatment. [16]

The positive effect of prenatal corticosteroids on RDS in clinical settings is further confirmed by the findings of a research by Eriksson et al. The risk of Sudden Infant Death Syndrome, late neonatal death, bronchopulmonary dysplasia, respiratory distress syndrome, intraventricular hemorrhage, and cerebral palsy was lower in exposed newborns after adjusting for confounding factors.[17] An antenatal steroid birth interval of 24 hours to seven days is highly related with a decreased risk of intraventricular hemorrhage in extremely low birth weight infants, according to a study by Fortmann et al.[18] As per another study, antenatal steroid administration decreases neonatal mortality in infants delivered at gestation < 37 weeks.[19] In addition, evidence from Wang et al. suggests that ACS decreases the requirement for endotracheal tube placement and the use of exogenous surfactant in very low birth weight (VLBW) preterm newborns. Multiple-dose ACS newborns were less likely to receive surfactant and had a lower rate of intubation compared to their non-ACS counterparts. Intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, sepsis, and

chronic lung disease all occurred at the same rates regardless of whether the infant received a single dosage of ACS or many doses, or if they were given betamethasone or dexamethasone.[20]

On a contrary, a study by Porto et al. suggests that the incidence of respiratory disorders is not affected by antenatal administration of steroids after 34 weeks' gestation. Antenatal treatment with corticosteroids at 34-36 weeks of pregnancy does not reduce the incidence of respiratory disorders in newborn infants.[21] Bonanno et al also concluded that antenatal corticosteroids have proven effective for singleton pregnancies at risk for preterm birth between 26 and 34 weeks gestation, questions remain about the utility in specific patient populations such as multiple gestations, very early preterm gestations, and pregnancies complicated by intrauterine growth restriction.[5]

CONCLUSION

The present study revealed that patients with planned steroid administration suffered from significantly lower rates of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), pneumothorax, and mortality compared to those with unplanned antenatal steroid administration.

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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Erectile Dysfunction in Male Patients of Urethral Stricture Following Urethroplasty

Erectile Dysfunction with Urethral Stricture

Muhammad Owais Rafiq[1], Muhammad Ibrahim Shaikh[2], Raj Kumar[1], Waqas Ahmed Memon[1], Zubda Malik[1] and Ali Raza[1]

ABSTRACT

Objective: To determine the frequency of erectile dysfunction in patients with urethral stricture following urethroplasty operation.
Study Design: A case-based study.
Place and Duration of Study: This study was conducted at the Department of Urology, Liaquat National Hospital, Karachi from November 2019 to April 2020.
Materials and Methods: A total of 79 sexually active males with urethral stricture on X-Ray urethrogram requiring urethroplasty were recruited in this study. In all of these patients urethroplasty was performed. Patient was discharged on the second postoperative day with Foley's catheter and follow-up after 2 weeks for removal of Foley's catheter. After successful voiding patients was followed after 12 weeks for erectile function. Final outcome i.e. erectile dysfunction was observed after 12 weeks of surgery by using IIEF score. All data was recorded in predesigned proforma.
Results: The average of the age was 37.11±10.02 years. Frequency of erectile dysfunction in patients with urethral stricture following urethroplasty was 34.18% (27 of 79). Rate of erectile dysfunction in patients with urethral stricture was statistically significant among age groups of the patients (p=0.036).
Conclusion: The data indicate that ED occurs after urethral reconstruction for the repair of urethral strictures. Location of the stricture and the age of patients were identified as the risk factors for ED. The posterior urethral stricture have a particularly strong association with erectile dysfunction.
Key Words: Urethral stricture, Erectile dysfunction, Urethroplasty

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INTRODUCTION

Urethral stricture disease (USD) is among the commonest and earliest described urological conditions, leading to considerable disability. It has perplexed surgeons for a long time[1,2]. Developed nations estimate a prevalence of 0.6%, which is likely greater in undeveloped nations.[3] For management, various surgical interventions have been proposed, e.g. primary anastomotic urethroplasty, substitution urethroplasty, and direct visual internal urethrotomy.[4]

A particularly concerning outcome of urethroplasty is erectile dysfunction (ED). Postoperative ED (PED) significantly impacts overall patient satisfaction with the procedure[4,5]. The outcomes and accomplishments of reconstructive urethroplasty have been thoroughly studied from the clinicians' perspective, e.g., improvement as seen on flowmetry, etc. However, failure to acknowledge and incorporate patient perceptions such as impact on sexual wellbeing and mental health is prevelant. Self-reports are the only metric available to gauge the effects of adverse postoperative outcomes on quality of life.[6,7]

There has been long-standing discourse regarding this subject. The estimated prevalence of ED in males > 20 years is reported to be 10% to 20%, with most reports leaning towards 20%.[8] In patients suffering from USD the prevalence of ED post-urethroplasty is approximately 2.3%. With regards to urethroplasty for repair of anterior urethral strictures (AUS), buccal mucosa graft (BMG) urethroplasty (originally presented by Humby, 1941)[9] and anastomotic urethroplasty (originally presented by Jordan et al., 1914)[10] are the most frequently performed. ED is either organic or psychogenic. Anatomically, the cavernous nerves are in close approximation to the proximal urethra, where they arise from the floor of the pelvis.

The focus of this research is to determine the frequency of ED following urethroplasty for USD. PED is

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observed within our practice on patient follow-ups and we find this an apt topic of study taking into account the relative novelty of the procedure in Pakistan and the lack of published local data. The findings of this study may impact technical aspects of urethroplasty procedures such as site of incision, technique of approach, and catheter retention time.

MATERIALS AND METHODS

A case-based study was conducted at the Department of Urology, Liaquat National Hospital, and Karachi, Pakistan, between November 2019 and April 2020. A Non - probability consecutive sampling was employed to recruit participants.

The sample size was calculated using the WHO software, taking the prevalence of erectile dysfunction based on IIEF-5 criteria before surgery. (P) = 28.5%, [8] margin of error =10%, and confidence level 95%. A total of 79 study participants were required. All patients aged between 20 to 50 years, who were willing to undergo intervention and follow-up and those who were sexually active males (on history) with urethral stricture (on X- Ray urethrogram) requiring urethroplasty were included in the study. Patients having recurrent urethral stricture (was confirmed by history), those who refused to complete the erectile function questionnaire, and those with uncontrolled hypertension, diabetes mellitus, and other major medical comorbidities were excluded from the study.

All patients visited the department of urology, Liaquat National Hospital, Karachi and following the inclusion criteria was included in the study. Ethical approval was obtained from the institutional review committee. An informed consent was taken prior to enrolment of patients in the study. In all these patients urethroplasty was performed by the consultant urologist with experience of more than 5 years. Patient was discharged on the second postoperative day with folley's catheter and follow-up after 2 weeks for folley's removal. After successful voiding patients were followed after 12 weeks for erectile function. In an attempt to more comprehensively assess erectile function and satisfaction after urethroplasty. Patient's response was evaluated after 12 weeks postoperatively. After discharge, all patients were followed up. Final outcome i.e. erectile dysfunction was observed after 12 weeks of surgery by using IIEF score as per operational definition. All data was recorded by a principal investigator on a predesigned proforma. Biasness and confounder was controlled by strictly following the inclusion criteria.

SPSS version 21 was used for data compilation and analysis. Frequencies and percentages were computed for qualitative variables like urethra (anterior/posterior) and erectile function (12 weeks as y/n). Quantitative variables were presented as mean ± SD like age, length of stricture and erectile function score (12 weeks). Effect modifiers like age, urethra and length of stricture were controlled through stratification. Chi-square test was used. P value ≤0.05 was considered as significant.

RESULTS

A mean age of 37.11 ± 10.02 years was observed. The mean length of stricture was 2.41 ± 0.43 cm. The frequency of erectile dysfunction in patients with urethral stricture following urethroplasty was 34.18% (27/79) (Table 1).

Table No.1: Demographics of the study participants

Parameters	**N (%)**
Age (in years)	37.11 ± 10.02
Length of stricture (cm)	2.41 ± 0.43
Erectile function score	20.38 ± 5.70
Age groups	
21-30	24 (30.38%)
31-40	25 (31.65%)
41-50	30 (37.97%)
Urethra status	
posterior urethra	46 (58.23%)
anterior urethra	33 (41.77%)
Erectile dysfunction	
yes	27 (34.18%)
no	52 (65.82%)

Rate of erectile dysfunction in patients with urethral stricture was statistically significant among age groups of the patients (p=0.036) while the difference was not statistically significant in urethra status or the length of stricture (Table 2).

Table No.2: Stratification of Erectile Dysfunction with Age, Urethra Status and Length of stricture

Parameter		**Erectile Dysfunction**	
	Yes	No	P-Value
Age Groups (Years)			
21 to 30	4 (16.7%)	20 (83.3%)	0.036
31 to 40	8 (32.0%)	17 (68.0%)	
41 to 50	15 (50.0%)	15 (50.0%)	
Urethra			0.893
Anterior	11 (33.3%)	22 (66.7%)	
Posterior	16 (34.8%)	30 (65.2%)	
Length of Stricture			
≤ 2.5	18 (32.7%)	37 (67.3%)	0.681
>2.5	9 (37.5%)	15 (62.5%)	

DISCUSSION

Urethral stricture disease (USD) has a prevalence of 229-627 per 100,000 males i.e. approximately 0.6% of the male populace at risk. The population at greatest risk are elderly males. The effects of USD greatly impact individual standard of living for men as well as of their partners.[11] According to Santucci et al. the geriatric male population suffers from USD most frequently and the incidence rises beyond the 55 year mark. USD can be treated in a large majority of patients

with urethral reconstructive surgery. These procedures have been documented to be very successful i.e. > 90%.[12] Of these procedures urethroplasty results in a lower rate of adverse outcomes and is associated with higher patient contentment.[13] Regardless, one very damaging outcome is ED, the incidence of which is 16.2% to 72% as per recent data.[14]

This study recruited 79 sexually active males, aged 20 to 50 years with USD as identified via x-ray urethrogram that were eligible for urethroplasty. The purpose was to determine the frequency of ED as an adverse outcome of the urethroplasty in these patients. The average age, and length of stricture of the participants were 37.11±10.02 years, and 2.41 ± 0.43 cm respectively. There were 30 (37.97%) posterior urethral strictures (PUS) and 49 (62.03%) anterior urethral strictures (AUS). Dharwadkar Sachin et al. reported that among their 48 participants aged 39.6±17.3 years, 83.3% had AUS and 16.7% had PUS.[15]

A recent study by Palminteri et al. assessed clinical details of approximately 1,500 male patients aged 2 years to 84 years with regards to USD that had been advised to follow up in specialized urogenital reconstruction facilities. The mean age of these patients on presentation with USD was 45.1±16.1 years. Majority of the strictures were present in the anterior urethra (92.2%) specifically the bulbar part (46.9%).[16]

In 2001, Coursey et al. reported data after assessing ED post-urethroplasty. The first study of its kind, this retrospective multicenter study evaluated 250 male patients. 30% of the participants had disclosed experiencing ED symptoms postoperatively to some extent. This study by us showed this frequency to be 34.18% (27/79). This frequency varies in the literature and seems to be subject to surgical procedure, site of stricture, and size of stricture.[17] Our study found ED to be present in 28.6% of the participants with AUS and 43.3% of those with PUS.

A longitudinal study conducted by Eltahawy et al. on 260 male patients post-anterior urethral reconstructive surgery showed that 2.3% (6/260) patients with previously healthy and normal erectile functioning reported ED[18].

It is well established that psychologic and neurologic factors greatly impact erectile functioning. Psychometric and neurologic assessments were not conducted and this is a significant limitation of our study. A statistical evaluation of the correlation between duration of disease and adverse outcomes of intervention was also not conducted; a further limitation.

CONCLUSION

The data indicate that ED occurs after urethral reconstruction for the repair of urethral strictures. Location of the stricture and the age of patients were identified as the risk factors for ED. The posterior urethral stricture have a particularly strong association with erectile dysfunction. These results may be relevant to the medical and surgical management of patients with urethral strictures. Erectile function should be assessed and documented in each patient before urethroplasty.

Author's Contribution:

Concept & Design of Study:	Muhammad Owais Rafiq, Muhammad Ibrahim Shaikh
Drafting:	Raj Kumar, Waqas Ahmed Memon
Data Analysis:	Zubda Malik, Ali Raza
Revisiting Critically:	Muhammad Owais Rafiq, Muhammad Ibrahim Shaikh
Final Approval of version:	Muhammad Owais Rafiq, Muhammad Ibrahim Shaikh

Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Microbiological Patterns Among Neonates Suffering from Late Neonatal Sepsis and to Specify the Antibiotic Susceptibility

Bacteriological Profile and Antibiotic Susceptibility in Neonatal Sepsis

Sana Arshad[1], Athar Razzaq[1], Ejaz Ahmad[1], Muhammad Ali[1], Muhammad Rashid Shabeer[1] and Kiran Abbas[2]

ABSTRACT

Objective: To assess the microbiological patterns among neonates suffering from late neonatal sepsis and to specify their antibiotic susceptibility.

Study Design: A retrospective study

Place and Duration of Study: This study was conducted at the Department of Neonatology Department Of Recep Tiyyap Erdogan Hospital Muzafargarh between 1st January 2016 and 1st January 2021.

Materials and Methods: All medical records of neonates who developed or presented after a stay of 48 hours in a hospital setting and presented with signs and symptoms of sepsis and their blood cultures reported between 1st January 2016 and 1st January 2021 were included in the study. Data was retrieved from REDCap and analyzed by using SPSS version 26.0.

Results: A total of 103 (23.9%) patients' blood cultures were found positive, and of these, 38 (36.3%) were coagulase negative staphylococci, 5 (4.8%) were Actinobacteria, 7(6.8%) were E.coli, 17(16.5%) were Klebsiella pneumoniae, 13(12.62.%) were Pseudomonas aeruginosa, 18 (17.4%) gram positive cocci, 2 (1.94%) were streptococcus, 1(0.97%) proteus vulgaris, 1 (0.97%) MRSA, and 1 (0.97%) were enterococcus species. It is observed that overall microbes show high resistance towards common antimicrobials, including ampicillin, amoxicillin, cefotaxime, tobramycin, and ceftazidime.

Conclusion: The results of this study clearly show that the microbes are resistant to commonly available antibiotics and hence antibiotic stewardship is necessary in resource poor countries like Pakistan.

Key Words: Antibiotic Susceptibility, Neonatal Sepsis, MRSA

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INTRODUCTION

Birth asphyxia, prematurity, and neonatal sepsis are the three main causes of neonatal mortality worldwide.[1] Traditional classifications of sepsis include early-onset (occurring within 72 hours of birth) and late-onset sepsis (beyond 72 hours). The majority of late-onset infections are caused by hospital-acquired organisms, in contrast to early neonatal infections, which are typically acquired by maternal vaginal tract germs.

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Late onset sepsis can be community acquired, but the majority of cases are of hospital acquired infections. In South Asian healthcare data, the cumulative incidence of culture-positive sepsis was 15.8 per 1000 live births (95% CI 12.7 to 18.8, n=15 reports). This is roughly two to four times more than what is recorded in upper income nations like the United States and Uk.[2,3] In comparison to developed countries, it is 4 to 10 times greater.[2,3]

This overall scenario is a result of poverty, inadequate access to appropriate interventions, especially facility births, and egregious inequality in the provision of healthcare. Most hospital acquired infections are documented in wealthy countries among significant numbers of very high risk, extremely low birthweight (1000 g) infants who frequently go unresuscitated in undeveloped countries.[4] In many developed countries, coagulase-negative staphylococci (CONS) and gram-positive bacteria are the main causes of late-onset newborn sepsis, while gram-negative bacteria are more frequently responsible in underdeveloped nations. The variety of microorganisms that cause late-onset

newborn sepsis varies geographically and with time in the same location. [5,6]

According to an article by M Jeeva Sankar and colleagues, one of the most prevalent organism type was a gram-negative one (63%) with the top three being Klebsiella spp. (23%), Escherichia coli (14%), and Acinetobacter spp. (8%) Staphylococcus aureus and Coagulase-negative Staphylococci made up 20% and 9%, respectively, of the Gram-positive bacteria. Gram negative bacteria had a greater mortality rate than Gram - positive cocci (11.9%; 95% CI 10.5 to 13.3%). The most prevalent bacteria among the 703 isolates from community - based settings were Klebsiella spp (25%), E coli (15%), and S aureus (12%).[7] In the last decade, it has been observed that there is high antibiotic resistance among gram–negative hospital acquired neonatal sepsis. Isolates are about 60 -70% multidrug resistant. [8]

As our hospital is looking after both inborn neonates as well, we also take care of referrals. We found that there is tremendous antibiotic resistance particularly among the neonates that are being referred from both private and government institutes in the current study, investigators aimed to examine the microbiological patterns of late neonatal sepsis and to specify their antibiotic susceptibility. We have aimed to see which etiological agents are responsible for late onset sepsis and their resistance pattern. The objective of this study was to assess the microbiological patterns among neonates suffering from late neonatal sepsis and to specify their antibiotic susceptibility.

MATERIALS AND METHODS

A retrospective study was undertaken at the Department of Neonatology, Recep Tiyyap Erdogan Hospital Muzafargarh. Exemption from ethical approval was granted by the institute review board of Indus Hospital and Health Network with reference # IHHN_IRB_2021_08_013.

Data and medical records of the neonates were extracted from the hospital's database after the administration's approval was obtained. All cases of neonatal admissions to Neonatal ICU with suspicion of neonatal sepsis between 1st January 2016 and 1st January 2021 were included in the study.

All neonates who developed or presented after a stay of 48 hours in a hospital setting and presented with signs and symptoms of sepsis and their blood cultures reported were included in the study. Neonates with marked dysmorphism and complex congenital heart diseases were excluded. Blood cultures were taken for all neonates with suspected late onset clinical sepsis. Clinical sepsis was defined as the presence of any of the signs suggestive of sepsis clinically. such as lethargy, apnea, tachypnea, tachycardia, hypotension, temperature instability, poor feeding, poor perfusion, abdominal distension, plus positive septic screen. [9]

Approximately 1 ml of blood was obtained for culture with antiseptic precautionary measures from a vein in the arm as well as a central vein. Using a Peds Plus Vial, a BACTEC 9050 automated device carried out the culture. Gram staining was done for any culture that showed a positive result, and subcultures were carried out on the proper media based on the results of the Gram stain: Mac Conkey agar and 5% sheep blood agar for Gram negative and positive organisms, and Sabouraud's dextrose agar and 5% sheep blood agar for yeast isolates. All negative containers were cultured once on blood agar and then discarded after being incubated in the apparatus for up to seven days. [6]

Data was retrieved from REDCap and analyzed by using SPSS version 26.0. Qualitative data is presented in terms of frequencies and percentages, and quantitative data is presented in terms of mean and standard deviation

RESULTS

During the study period, 430 patients' blood cultures with clinically suspected sepsis were sent, out of which 103 (23.9%) patients' blood cultures were found positive .The following results are of positive blood cultures in neonates. The mean gestational age of the neonates having positive blood cultures was 34 □ 3.121, with a minimum age of 26 weeks and maximum age of 42 weeks. The mean weight of patients in grams was 2129 □ 850.035 grams, with a minimum weight of 745 grams and a maximum weight of 5000 g.

Table No.1: Perinatal Parameters of the Subjects

Variable	Values	
Gestational Age (Mean □□SD)	34 □ 3.121	
Gestational age groups	26-36.6 weeks	82 (79.6%)
	37-41.6 weeks	20(19.41%)
	Greater than 42 weeks	1 (1%)
Weight	2129 □ 850.035 grams	
Gender	Male	63(63%)
	Female	40(38.83%)
Duration of rupture of membranes	Less than 12 hours	87(84.5%)
	Greater than 12 hrs	16 (15.5%)
Mode of Delivery	c section,	57 (55.3%)
	SVD	46(44.7%)
Place of Delivery	Our setup	63 (61.2%)
	Other setups	40(38.8%)

Regarding the gestational age, 82 (79.6%) were between the ages of 26-36.6 weeks, 20 (19.41%) neonates were between 37-41.6 weeks, and only 1 (1%) had a gestational age greater than 42 weeks. The majority of the patients were males, 63 (63%), and 40(38.83%) were females. 16 (15.5%) patients had ruptured membranes for greater than 12 hours, whereas 87 (84.5%) had ruptured membranes for less than 12 hours. Regarding liquor, 90(87.4%) had clear liquor, whereas 13(12.6%) had meconium-stained liquor.

The majority of the neonates were delivered via c section, 57 (55.3%), whereas 46(44.7%) were delivered via SVD. 63 (61.2%) neonates were delivered at our setup, whereas 40 (38.8%) were delivered at other setups and were referred to our hospital. 78 (75.7%) had births attended by trained personnel, whereas 25 (24.3%) had no trained birth attendant at the time of birth.

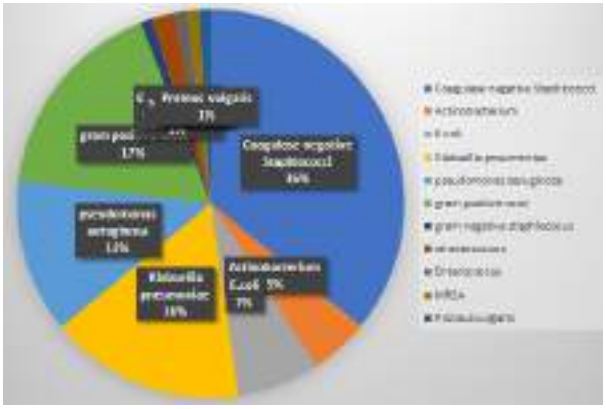

Figure No.1: Distribution of Bacterial Organisms Found in Cultures Among Neonates

Table No.2: The Results of Sensitivity and Resistance to Specific Drugs

Antibiotics	Sensitive	Resistant
Ampicillin	20(20%)	80(80.%)
Amoxicillin	31(31%)	69(69%)
Gentamicin	66(66%)	34(34%)
Amikacin	85(85%)	15(15%)
Tobramycin	36(36%)	64(64%)
Cefotaxime	34(34%)	66(66%)
Ceftazidime	37(37%)	63(63%)
Meropenem	67(67%)	33(33%)
Imipenem	63(63%)	37(37%
Cefoperazone Plus Sulbactam	58(58%)	42(42%)
Chloramphenicol	70(70%)	30(30%)
Piperacillin/Tazobactam	59(59%)	41(41%)
Colistin	64(64%)	36(36%)
Ciprofloxacin	64(64%)	36(36%)
Co-trimoxazole	36(36%)	64(64%)
Ertapenem	42(42%)	58(58%)
Ceftriaxone	47(47%)	53(53%)

Out of the 103 positive cultures, 38 (36.3%) were coagulase negative. Staphylococci 5 (4.8%) were Actinobacteria, 7(6.8%) were E.coli, 17(16.5%) were Klebsiella pneumoniae, 13(12.62.%) were Pseudomonas aeruginosa, 18 (17.4%)) gram positive cocci, 2 (1.94%) were streptococcus, 1(0.97%) proteus vulgaris ,1(0.97%) MRSA ,1(0.97%) were enterococcus species as illustrated in the Figure 1.

The susceptibility and resistance pattern are presented in Table 2. It is observed that overall microbes showed high resistance towards common antimicrobials including ampicillin, amoxicillin, cefotaxime, tobramycin, and ceftazidime.

DISCUSSION

Neonatal sepsis is a major health concern in developing countries such as Pakistan. [10] Timely diagnosis and prompt administration of empirical antibiotics is necessary while the results of the blood culture are awaited. The range of organisms that cause newborn sepsis evolves over time and also differs by area. Regular assessment for microbiological species and vulnerability patterns can eliminate any confusion about the treatment strategy for treating newborn sepsis, allowing an acceptable choice of antibacterial drugs for initial therapy to be outlined and re-evaluated in a timely fashion.[11]

In our study, 16 (16%) were coagulase negative staphylococci in this study, and they are the most common organisms isolated in the present study. Contrary findings were reported by several other authors including Bhat et al. (90.8%) and Shrestha et al. (60.64%). [12,13]

The low prevalence of CoNS infection in the current study, which is typically linked to central lines, and the rarity of Group B Streptococcus infection in Pakistan can both be blamed for the low frequency of gram-positive infection.[5] In neonatal sepsis, Pseudomonas aeruginosa was found in 13% of patients in our study. Another study from south India (33.2%) produced similar findings.[12] While another research claimed that Klebsiella was the most prevalent organism. [14] Staphylococcus aureus was cited by some writers as being the most prevalent organism. [15] Additionally, the bacterial flora that causes early-onset newborn sepsis has undergone a significant alteration as a result of intrapartum antibiotic prophylaxis.

The current study's low rate of enterococci disease (1%) is comparable to the findings of Bhat et al. (2.2%). [12] In polymicrobial sepsis, the connection of two distinct species did not follow any particular pattern. It's possible that a newborn already sick with one microbe picked up the second one from the hospital setting, or that both of the bacteria were picked up there. Most earlier research either did not recognize the importance of polymicrobial sepsis or did not take into account the second organism in a culture that was already

positive.[16] The incidence of polymicrobial sepsis was not studied in this research.

In a study published recently by Pokhrel et al., a total of 69 (20.5%) neonates who were admitted to the NICU had culture-positive sepsis. [17] Out of these, 47 (68.1%) were preterm babies. The majority of the bacteria isolated were gram-negative, with Klebsiella species making up the majority (n = 23, 33.3%). Klebsiella was found to be resistant to typically used antibiotics, including Cefotaxime, Gentamicin, Ciprofloxacin, Ofloxacin, and Chloramphenicol. [17]

The prevalence of polymicrobial sepsis and the clinical outcome of newborn septicemia must be correlated. The issue of antibiotic resistance is pervasive. [18-20] Numerous Gram positive and Gram negative microorganisms in the current investigation also displayed varied resistance to many of the therapeutically helpful medicines. Recent studies have also noted the increased incidence of resistance to routinely used antibiotics. The current study shows that the commonly used antibiotic ampicillin is resistant in about 80% of cultures and that chloramphenicol is sensitive in about 70% of cultures.

There are, however, some limitations to this study. Firstly, it is a retrospective study conducted at a single center. Moreover, the classification of sepsis (early/late sepsis) has not been taken into consideration. In addition to these limitations, individual microbes' drug sensitivity has also not been taken into consideration in this study.

CONCLUSION

We conclude that neonatal sepsis is a grave medical problem in our region. The results of this study clearly show that the microbes are resistant to commonly available antibiotics and hence antibiotic stewardship is necessary in resource poor countries like Pakistan.

Author's Contribution:

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Original Article

Frequency and Risk Factors of Lipohypertrophy in Insulin Treated Patients with Diabetes: An Experience from a Tertiary Care Center in Multan

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ABSTRACT

Objective: The present study aimed to evaluate the frequency and risk factors of lipohypertrophy in insulin treated patients in a tertiary care center in Multan.

Study Design: cross sectional descriptive study

Place and Duration of Study: This study was conducted at the Diabetic Outdoor of Nishtar Hospital, Multan between 1st January 2022 to 31st June 2022.

Materials and Methods: We included 360 patients, taking insulin for more than one year in our study. The patients were interviewed about insulin injection habits and the injection sites examined according to a preformed questionnaire.

Results: We included 360 patients with diabetes mellitus who used insulin for more than one year. The frequency of lipohypertrophy was 43.6%. Mean duration of diabetes and mean duration of insulin use were 14.68±7.62 years and 8.45±6.1 years, respectively. Longer disease duration, longer insulin use, higher doses, use of ice cold insulin and lack of rotation of injection site were the major risk factors of lipohypertrophy.

Conclusion: Lipohypertrophy is a common complication of insulin use related largely to improper injection technique. Patient education and frequent examination of the injection site can help prevent lipohypertrophy.

Key Words: Diabetes mellitus, insulin, lipohypertrophhy, injection site.

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INTRODUCTION

Diabetes mellitus (DM), a major public health problem, affects 536.6 million adults globally. This is estimated to increase to 700 million by 2045.[1] Insulin is an essential medication for all patients with type 1 diabetes. Many patients with type 2 diabetes ultimately need insulin as well.[2]

In order to optimize glucose control and insulin use safety, it is crucial to teach the correct insulin injection technique to all patients and care givers. Insulin must be injected into the subcutaneous tissue in the abdomen, thigh, buttock or upper arm.

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A shorter needle length (4 mm) in pen and a 6 mm needle in syringe is recommended to avoid accidental intramuscular injection. The skin should be raised by the thumb and index finger to make a fold and insulin injected slowly at 90 degree angle. The patient should count to 10 before withdrawing the needle. Use of short needles and injection site rotation should be taught to all patients and care givers.[3]

In addition to hypoglycemia, a major adverse effect of insulin therapy, there are a number of side effects related to insulin administration. These include local pain and discomfort, bruising, infection, needle stick injuries and lipodystrophy.

Lipodystrophy (LD) is the most frequent local complication of insulin administration and may present either as lipoatrophy (LA) or lipohypertrophy (LH). LA manifests as skin indentation and is thought to be due to lipolytic reaction to impurities in insulin preparation. Since the advent of purified insulin, its prevalence has dropped to only 1- 2%.[4] Lipohypertrophy, on the other hand is still, fairly common. A recent meta- analysis has shown the pooled prevalence of LH as 38%.[5] Other studies have reported the prevalence as 37.3- 53.1%.[6-8] In a recent Indian study, the prevalence of LH in patients with Type 1 Diabetes mellitus was as high as 69.8%.[9]

Lipohypertrophy presents as a firm swelling of the sub cutaneous tissue and results from the growth promoting properties of the insulin molecule combined with incorrect insulin administration. Failure to rotate insulin injections, use of ice cold insulin, use of long needles, increased insulin dose and prolonged duration of insulin therapy are the predisposing factors for development of LH.[10] LH is diagnosed by visual observation and palpation of insulin injections sites, using tangential light and different patient angles. A lubricant gel can be used, if needed.[11,12] Injection into LH site leads to erratic insulin absorption and high glycemic variability.

Lipohypertrophy can be prevented by targeted education of patients and their care givers. All insulin using patients should have their injection sites checked at regular intervals, both visibly and by palpation, for detection of LH. All patients must be instructed to correctly rotate injection site which means that injections are spaced at least 1cm (an adult finger breath from each other).[3] LH lesions have been shown to regress significantly after 6 months of systematic rotation and single use of needles.[13]

MATERIALS AND METHODS

It was a cross sectional descriptive study, including 360 patients from the diabetic outdoor department of Nishtar Hospital, Multan, using non probability sampling technique. Study was done from 1st January 2022 to 31st June 2022. All diabetic patients more than 12 years old, taking insulin for more than one year were included in the study. Patients with gestational diabetes were excluded. Informed consent was taken from all patients. Clinical history about the type and duration of diabetes, type (basal-bolus or premixed) and duration of insulin use, technique of insulin use including site (abdomen, thigh, buttock or arm), rotation of injection site, type of insulin device (insulin syringe or pen), needle length, reuse of needle and use of cold insulin was enquired. Patients were also asked other injection site reactions like bruising, pain, redness, leakage, and swelling.

Lipohypertrophy was determined by clinical examination. All the injection sites were inspected from various angels using tangential light in both upright and supine position. The relevant site was also palpated and an area of skin suspected for LH was pinched to identify difference in thickness or texture from the surrounding skin. Lack of insulin rotation was defined as injecting insulin in the same region or keeping less than a finger breath distance between consecutive insulin injections. Reuse of insulin needles was defined as use of a needle more than once. The frequency of needle reuse was further classified according to the number of times the needle was reused.

Approval from ethical review committee of Nishtar Medical University was taken. Data was entered and analyzed by SPSS-23. Mean and standard deviation of descriptive variables, like age, duration of diabetes, duration of insulin use, and daily dose of insulin was determined. For comparison among different groups Chi square test was applied, and P value <0.05 was considered statistically significant.

RESULTS

We included 360 patients with diabetes mellitus who used insulin for more than one year. Among these, 149 (41.4%) patients were male and 211 (58.6%) were female. Mean age of these patients was 50.75±11 years. Of these, 196 (54.4%) patients were uneducated, 65 (18.1%) had primary education, 47 (13.1%) middle school, 29 (8.1%) high school, and only 23 (6.4%) patients had university level education.

Of 360 patients, 322 (89.4%) had type 2 DM and 38 (10.6%) patients had type 1 DM. Mean duration of diabetes and mean duration of insulin use was 14.68±7.62 and 8.45±6.1 years, respectively. Mean daily insulin dose was 63.6±18 units. Most of the patients were using Human insulin (78.6%). Insulin syringe was the preferable device (92.2%) for injection. Majority of the patients injected insulin in the abdomen (68.3%). The reuse of the insulin needle was fairly common (98.3%). Only 233 (64.7%) patients had received education about the technique of injecting insulin.

Table No.I: Insulin injection habits of study participants

Characteristics		No of patients	Percentage%
Insulin Regimen	Pre-mixed	288	80
	Basal-bolus	72	20
Type of insulin	Human	283	78.6
	Analogue	77	21.4
Location of injection site	Abdomen	246	68.3
	Thigh	25	6.9
	Arm	9	2.5
	Mixed	80	22.2
Rotation of insulin injection	Yes	340	94.4
	No	20	5.6

Reuse of insulin injection	Never	6	1.7
	2-4	40	11.1
	5-7	195	54.2
	8-10	76	21.1
	>10	43	11.9
Needle length(in mm)	4	7	0.19
	5	84	23.4
	6	269	74.7
Injection device	Pen	28	7.8
	Syringe	332	92.2
Use of ice-cold insulin	Yes	280	77.8
	No	80	22.2
Injection giver	Self	307	85.3
	Care giver	53	14.7
Other side effects at injection site apart from lipohypertrophy	Bruising	59	16.4
	Pain	100	27.8
	Lipoatrophy	53	14.7
	Redness	38	10.6

Table No.2: Factors associated with lipohypertrophy

Risk factors		Lipohypertrophy		P value
		Yes	No	
Gender	Male	70	79	0.279
	Female	87	124	
Education	None	85	111	<0.001
	Primary	33	32	
	Middle	23	24	
	High school	2	27	
	University	14	9	
Type of DM	Type 1	22	16	0.060
	Type 2	135	187	
Duration of disease (years)	>10	113	108	<0.001
	≤10	44	95	
Duration of insulin use (years)	>8	93	64	<0.001
	≤8	64	139	
Daily dose of insulin (units)	>40	151	166	<0.001
	≤40	6	37	
Insulin regimen	Premixed	129	159	0.366
	Basal-bolus	28	44	
Insulin type	Human	115	168	0.029
	Analogue	42	35	
Insulin device	Syringe	136	196	<0.001
	Pen	21	7	
Rotation of injection site	Yes	143	197	0.014
	No	14	6	
Reuse of insulin Needle (number of times)	Never	0	6	0.143
	2-4	15	25	
	5-7	93	102	
	8-10	31	45	
	>10	18	25	
Needle length(mm)	4	7	0	<0.001
	5	56	28	
	6	94	175	
Use of Ice cold insulin	Yes	129	151	0.078
	No	28	52	

Other injection habits of the participants are summarized in table I.

Lipohypertrophy was present in 157 (43.6%) patients. Of these, 80 (50.9%) patients had single lump on examination while 77(49.04%) patients had multiple lumps. Most of the studied patients had never examined the injection site (56.4%). Only 17 (4.7%) patients had their injection site examined by their health care provider regularly.

The association of various risk factors with LH is presented in Table 2. Longer disease duration, longer insulin use, higher doses, use of ice cold insulin and lack of rotation of injection site were the major risk factors of lipohypertrophy.

DISCUSSION

The frequency and risk factors affecting LH in insulin using diabetic patients was investigated. In our study, lipohypertrophy was present in 43.6% patients. A recent meta-analysis had shown the pooled prevalence of LH as 38%[5]. In Turkey, Ireland and Italy the prevalence was 48.8%, 51% and 48.7% respectively, similar to our study[14-16]. The prevalence of LH in Blanco's study[17] was much higher (64.4%) while in a Canadian study, it was 24.6%, much lower than our study.[18]

In this study, LH was more common among Type 1 diabetics (57.9%) than in type 2 diabetic patients (41.9%). Omar and his colleagues found the prevalence of LH as 54.9% in type 1 diabetes[19]. In another study, it was 52.3%.[20] These are comparable to our study results. In a recent Indian study, the prevalence of LH in patients with Type 1 DM was as high as 69.8%[9]. In Youssef's study of type 1 diabetics, only 23.7% had LH. [21] In Ajlouni's study, the prevalence of LH in Type 2 DM was 35.3%.[6] This inconstancy may be related to patient factors as well as variation in examination methods and skills of the health care provider examining the patient in different studies. LH was more common in male (47%) than in female (41.2%), but this difference was statistically insignificant. In other studies, the effect of gender was not significant as well.[8, 9, 22] In our study, lipohypertrophy was more common in older and less educated patients. In another study, no statistically significant effect of education was noted.[22]

In our study, longer duration of diabetes (>10years), longer duration of use of insulin (>8 years) and higher daily dose of insulin (>40 units per day) were significantly associated with lipohypertrophy. Other studies also confirm increased risk of lipohypertrophy with longer duration of diabetes.[9,15,17] The results of a study by Wjitcharoen et al were similar to ours in this regard.[22] Vardar and Kizici also found significant association of longer duration of insulin use and LH, which is comparable to our study.[14] Cunningham, however, did not find the total daily dose of insulin as a notable risk factor for LH.[15] In this study, insulin regimen (premixed/basal bolus) had no significant relation with LH formation. Use of insulin analogues, and use of insulin pen instead of syringe was associated with higher incidence of LH. In a study by Sunil Gupta, effect of both insulin regimen and type of insulin did not have a significant impact on LH formation.[9] Blanco and Omar also found that insulin type and device used for insulin injection was not significantly related to LH.[17,19]

In our study, LH was more prevalent among those who did not rotate injection site and in those who used longer needles. Cunningham and Blanco also found significant relationship between needle length and LH[15,17]. Although most of our patients (98.3%) reused insulin needles, we did not find a significant association between reuse of needles and LH. Gupta & Vardar studies found significant association of lack of rotation of injection site and reuse of injection needle on LH formation.[9,14]

CONCLUSION

We conclude that lipohypertrophy is a common local complication of insulin injection use. This is largely preventable with targeted education about injecting insulin and regular examination of insulin injection sites.

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Original Article

Prevalence of Beta Thalassemia Trait in Semi-Urban Population of Karachi

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ABSTRACT

Objective: To evaluate the prevalence of Beta Thalassemia Trait in Semi-urban Population of Karachi.
Study Design: Comparative Cross-sectional study
Place and Duration of Study: This study was conducted at the Department of Medicine, Baqai Medical University, Karachi and its affiliated teaching hospitals in Karachi, from July 2021 to September 2021.
Materials and Methods: A total of 578 individuals were included in study, who were admitted in the medical ward and visiting out patients department (OPD) of the teaching hospital (Medical and obstetrics departments) of the Baqai medical university, Karachi. Patients with evidence of active blood loss, an acute or chronic inflammatory disorder, malignancy, recent surgery or pregnancy were excluded from the study. Complete blood count (CBC) was performed in all include individuals by using sysmex hematology analyzer. Mentzler's index was calculated and applied to identify the beta thalassemia carriers. Difference between RBC parameters of normal and carrier population was also compared.
Results: The 42 (7.2%) individuals among study population were suspected to have beta thalassemia trait on basis of Mentzler's index. In normal population Mentzler's index was 19.92±4.55 and in beta thalassemia trait (carrier) Mentzler's index was 10.15±3.33. It reliably detected microcytosis (positive predictive value of 95.2%). Statistically significant difference ($p<0.05$) of RBC parameters was noted between normal and suspected carrier groups.
Conclusion: RBCs parameters can reliably be used to screen and target thalassemia carriers.
Key Words: Thalassemia, Thalassemia screening, Thalassemia trait, Thalassemia carriers

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INTRODUCTION

Thalassemia, a group of diverse hemoglobin synthesis disorders, are regarded as the commonest genetic disorders. It is characterized by decreased or no globin chain synthesis. Traditionally it is classified as alpha or beta thalassemia, depending upon which synthesis is affected. More clinically meaningful terminology of transfusion dependent or non-transfusion dependent are becoming acceptable. Severity also depend upon presence of concomitant other mutations like sickle cell mutation or hemoglobin E. β- Thalassemia major (transfusion dependent thalassemia) disturbs both the patient and his or her β-thalassemia carrier parents.

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Apart from arranging regular blood transfusion, iron chelation therapy also costs a lot. Iron overload affects multiple organs. It is more common in Mediterranean region, Indian subcontinent and Middle East.[1.] Migration has changed epidemiology of Thalassemia to some extent, after addressing communicable diseases. [2] World Health Organization (WHO) has identified control of hemoglobin disorders, particularly β-thalassemia as priority. About 1.5% of the world's population is β- thalassemia carriers with 60,000 β-thalassemia births every year.[1] It is estimated 5 to 7% of Pakistan's population is β- thalassemia carriers.[3] A documentary registry need to be developed to get actual situation of β- thalassemia carriers.

At Pakistan treatment centers for thalassemia major patients are developed which provide regular blood transfusion and iron chelation therapy. Majority of these centers are developed by non-governmental organizations. Some of these centers are established in memory of β- thalassemia affectees by their families. Pakistan Bait-ul-Mall also support such patients. On the other hands measures to prevent incidence of β-thalassemia major appear less active.[4] Marriage between β- thalassemia carriers produce 25% probability of β- thalassemia major child. Family marriages, especially marriages among 1st degree cousins, are important contributory factor in this regard.

Pre-marriage screening of β- thalassemia carriers and counselling could be an important preventive step.[3] At Punjab province of Pakistan legislation is underway for β- thalassemia carrier screening before marriage. We lack thalassemia prevention strategy at national level. Punjab Thalassemia Prevention Program, a government funded initiative, is providing some service.[5] Even at school age, screening may be done and family may be informed about carrier status.

The different test or modalities like Naked eye single tube red cell osmotic fragility test (NESOFT), Cell Counter based formulas, hemoglobin electrophoresis and high performance liquid chromatography (HPLC) are used for β- thalassemia carrier screening with different degree of sensitivity and specificity.[6] The Naked eye single tube red cell osmotic fragility test (NESOFT) standardization is difficult as it may involve human visual error.[7] Cost is an issue with hemoglobin electrophoresis and high performance liquid chromatography (HPLC). They are also not routinely available. These two factors make hemoglobin electrophoresis and high performance liquid chromatography (HPLC) ineffective for mass screening. The screening of parameters by cell counter based and calculation of various indexes by mathematical formulas is fast, automated, cost effective and technically correct.[8] Use of such formula started back in 1973.[9] Currently, cell counters based formula are widely used in many parts of the world to screen β- thalassemia carriers. We also conducted a β- thalassemia carrier screening study in semi-urban population of Karachi, Sindh using cell counter based formulas. Other hematological parameters of Complete blood count (CBC) were also analyzed. This is an attempt to enroll and educate β-thalassemia carriers.

MATERIALS AND METHODS

This Comparative cross sectional study was conducted in the Department of Medicine, Baqai Medical University (BMU) in Karachi, from July 2021 to September 2021. A total of 578 individuals were included in study, who were admitted in the medical ward for evaluation of anemia and/or β- thalassemia carriers and visiting out patients department (OPD) of the teaching hospital (Medical and obstetrics departments) of the Baqai Medical University, Karachi. These patients were willing to participate in this study with given written consent too. Patients with history of active blood loss, an inflammatory disorder (acute or chronic), cancers or malignancy, history of recent surgery or blood transfusions were excluded from the study. This study was approved by the ethics committee of Baqai Medical University (BMU) /Ref: BMU-EC/01-2021, dated 12 February 2021. Sample size was calculated by Raosoft Sample size calculator. [10] For the study, three millimeter (ml) of venous sample (blood) was collected in Ethylenediamine tetraacetic acid (EDTA; anticoagulant) test tubes. The Complete blood count (CBC) including haemoglobin (Hb%), packed cell volume (PCV), red blood cell (RBC) count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) was performed by using sysmex (XS-1000) hematology analyzer. The Red blood cell (RBC) or erythrocyte indices are useful for diagnosis of anemia or decreased hemoglobin concentration below normal (Hb-12-15.5 gm/dl in women and in males Hb-14-18 gm/dl) and types. Mentzler Index (1973): mean corpuscular volume (MCV)/ Red blood cell (RBC) count was applied to identify suspected Beta thalassemia carrier individuals. Mentzler Indexes (1973) quotient <13 was taken as cut off for Beta thalassemia carrier. If quotient less than 13 (Beta thalassemia carrier) and if the quotient of mentzers index more than 13 (iron deficiency anemia). This index is useful for diagnosis of type of anemia.[11] Statistical Package for the Social Sciences (SPSS) version 22 was used to analyze collected data. Relative descriptive statistics, frequency and percentages were calculated for categorical variables like gender and normal or suspected beta thalassemia carrier. Mean and standard deviation (Mean ± S.D) were calculated for quantitative variables like age, hemoglobin (Hb%), erythrocyte or RBC count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC). Independent sample t-test was applied to compare the difference in HB%, erythrocyte or RBC count, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration between normal and/or suspected Beta thalassemia carrier individuals.

RESULTS

Out of 578 enrolled individuals, 300 patients (51.9%) females and 278 (48.1%) were male, female to male ratio was 1.08 (1.08:1). Among these 42 (7.2%) subjects were suspected to have beta thalassemia trait, on basis of Mentzer index. Mean and standard deviation were calculated in both normal and suspected beta thalassemia trait group for Hemoglobin (Hb%), Packed cell volume (PCV), red blood cell (RBC) or erythrocyte count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC). Independent sample t-test showed statistically significant difference ($p< 0.05$) of Hemoglobin (Hb%) in normal individuals (11.12±2.53) and in beta thalassemia carrier (10.78±1.46), red blood cell (RBC) or erythrocyte count in normal individuals (4.12±0.71) and in beta thalassemia carrier (6.68±0.21), in mean corpuscular volume (MCV) in normal individuals (79.66±4.349) and in beta thalassemia carrier (55.57±3.01), in mean corpuscular hemoglobin (MCH) in normal individuals (26.27±4.197) and in beta thalassemia carrier (21.14±4.102), in mean corpuscular hemoglobin concentration (MCHC) in normal individuals (33.59±4.08) and in beta thalassemia carrier

(29.76±.85), and in Mentzler Index in normal individuals (19.92±4.55) and in beta thalassemia carrier (10.15±3.33). (Table. I). 40 out of 42 individuals of suspected beta thalassemia carrier had MCV≤ 76. (Positive predictive value = 95.24%).

Table No. I: Hematological parameters in normal and suspected beta thalassemia trait group

Parameter	Mean±SD in normal group (n=536)	Mean± SD In Suspected Beta Thalassemia Carrier (n=42)	p-value
Age (Years)	25.41±15.35	21.80±8.002	0.024
Hb (g/dl)	11.12±2.53	10.78±1.46	0.023
PCV(%)	34.38±18.63	37.19±9.87	0.05
RBC(10^6/µL)	4.12±0.71	6.68±0.21	<0.001
MCV(fl)	79.66±4.349	55.57±3.01	<0.001
MCH(pg)	26.27±4.197	21.14±4.102	<0.001
MCHC(g/dl)	33.59±4.08	29.76±.85	0.012
Mentzler Index	19.92±4.55	10.15±3.33	0.05

p-value< 0.05 significant, p-values>0.05 non-significant.

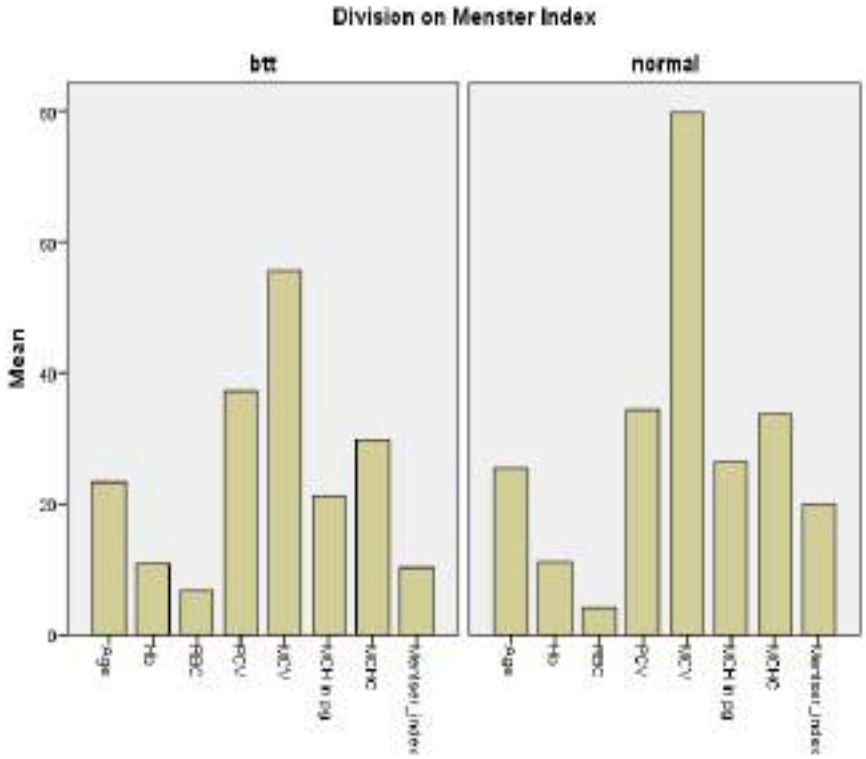

Figure No1: Graphical comparison of Hematological parameters in normal and suspected beta thalassemia trait group

DISCUSSION

Inexpensive diagnostic methods need to be developed for screening of β- thalassemia carriers, especially in developing or poor countries. People are reluctant for β-thalassemia carriers screening, not only due to financial reasons but also due to some social reasons. To declare someone suspected β- thalassemia carriers on basis of hemoglobin indices has long been discussed. Disproportionate decrease in mean corpuscular volume (MCV) and normal or slightly high red blood cell (RBC) count to raise suspicion of beta thalassemia carrier is well known.[5] One study published by Ferrara M et al in 2010 showed lower MCV value in β-thalassemia carriers than iron deficiency. When related to degree of anemia, β- thalassemia carriers had lower MCV than iron deficiency subjects with same hemoglobin level.[10,12] Parthasarathy V also concluded that mean corpuscular volume (MCV) < 76 fl and red blood cell (RBC) count > 4.9×10^{12}/L were associated with high probability of β- thalassemia carriers.[13] Our study had similar findings i.e MCV 55.57±3.01 and RBC count 6.68±0.21 in suspected β- thalassemia carriers. 95.24% of suspected β- thalassemia carriers had MCV <76, showing good positive predictive value. Karimi M et al concluded that MCH is more sensitive than MCV, for premarriage screening of β- thalassemia carriers(98.5 vs 97.6).[14] Study conducted by Bordbar E

et al also concluded that MCH is more sensitive than MCV.[15] In contrast to these results, Moafi A et al concluded MCV is more sensitive. They claimed MCV ≤ 80 can be used as cut off for screening β- thalassemia carriers. 4.1% of their study population, who were β-thalassemia carriers, had MCV ≥ 78 but ≤ 80. [16] Apart from β- thalassemia carriers and iron deficiency, other causes of microcytosis like alpha thalassemia trait, chronic diseases and sideroblastic anemia (although rare) may also alter sensitivity of these indices.[17] Therefore, instead of relying on single parameter, developing formula that include different indices can more sensitive to detect β- thalassemia carriers.[14] Different formula [(Mentzer index; MCV/RBC),(Srivastava;
MCH/RBC), (Ricerca; RDW/RBC) & (Green and King; MCV2×RDW/100 HB)] using RBC indices have varied sensitivities.[15] Pakistan is country with significant burden of thalassemia major. It can only be prevented or decrease by pre-marriage screening (Hb: electrophoresis) for beta thalassemia carrier. Accurate methods like hemoglobin electrophoresis and High Performance Liquid Chromatography (HPLC) are not suitable due to cost. Moreover, social norms do not permit or considers it bad, to think about disease on happy occasion. But use of Hb-electrophoresis or HPLC is not feasible due to cost and expertise needed. Apart from isolated hemoglobin indices analysis, to raise suspicion of β- thalassemia carriers, researchers have developed some formulas to raise suspicion about beta thalassemia carrier.

In our study, we utilized Mentzer index that showed raised suspicion of beta thalassemia carrier in 42 out of 578 individuals (7.2%) with positive predictive value of 95.24% for microcytosis. The results are comparable to previous studies. Importantly Pornprasert S et al found sensitivity and specificity of different varied among different populations.[18, 19] Variations at gene level may be responsible for that. Hence physician need to work to identify appropriate formula for their population. Algorithm may be developed to decide who could be candidate for hemoglobin electrophoresis on basis of CBC findings. This may ensure utilization of limited resources on right person. Kiss et al proposed an algorithm based on low MCV and ethnic background for screening purpose.[20] Their findings could not have been generalized because β- thalassemia carriers was more prevalent among one ethnic group of study population. But importantly they developed β-thalassemia carrier's probability table based on different values of MCV. They were in view that if β-thalassemia carrier's probability is > 20% based on their table, that person needs to be properly tested for β-thalassemia carriers. This may be the way to avoid over testing plus missing a person with β- thalassemia carriers. Amendolia et al probably used separation algorithms for first time, including support vector machine (SVM), to screen alpha and beta thalassemia carriers. It was in fact comparison of SVM and K-nearest neighbor (KNN) with a Multi layered Perceptron Classifier (MLP). Both techniques were 95% specific to distinguish thalassemia carriers from healthy individuals but MLP was slightly more sensitive than SVM.(95% vs 85%).[21] Roth et al also used single vector measurement for screening or raising suspicion for β- thalassemia carriers. They found all RBC parameter were significantly different between healthy individuals and β- thalassemia carriers. They developed a SVM formula using MCV and MCH, which was found highly sensitive. They compared their SVM results with different discrimination formula quoted in literature, and found that their SVM can reliably screen β- thalassemia carriers. They moved a step forward by comparing their formula with HPLC and Hemoglobin electrophoresis. They argued that both hemoglobin electrophoresis and HPLC can give false negative results if patient has iron deficiency or Hb level <9gm/dl. They found their formula was 99.56% sensitive in such cases.[22] Ahmed et al proposed algorithm for screening of β- thalassemia carriers in Pakistani population. They used one tube osmotic fragility test to raise suspicion of beta thalassemia carrier. Findings of one tube osmotic fragility test were compared to MCV and MCH. Test was found to be fairly sensitive. [23] Studies by Ansari et al[24] and Yazdani et al[25] showed similar results. This simple test, which does not need any expertise may be added to RBC parameters to make them more sensitive. It is recommended that Mass screening for beta thalassemia carrier at early age or during student life should be used and law for genetic counselling before marriage should be passed from parliament with strict implementation in our society that may help in prevention of thalassemia in Pakistan

CONCLUSION

RBCs indices can reliably raise suspicion of beta thalassemia carrier. Their reliability may further be enhanced by devising different formulas or their cut off for different populations due to genetic differences.

Author's Contribution:

Concept & Design of Study:	Adil Khan, Saqib ur Rehman
Drafting:	Amna Najeeb, Bushra Rabbani
Data Analysis:	Masooda Fatima, Saleem Ullah Abro
Revisiting Critically:	Adil Khan, Saqib ur Rehman
Final Approval of version:	Adil Khan, Saqib ur Rehman

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Original Article

Frequency of Graves Disease in Hyperthyroid Patients and its Associated Comorbidities

Graves Disease in Hyperthyroidism

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ABSTRACT

Objective: To find out frequency of Grave's disease in hyperthyroid patients and to measure the associated comorbidities in hyperthyroid patients.

Study Design: Descriptive Cross-Sectional study

Place and Duration of Study: This study was conducted at the Out Patient Department (OPD) of National Institute of Diabetes & Endocrinology (NIDE), Dow International Medical College Hospital (DIMC), and Medical Wards of Civil Hospital Karachi (CHK) from Jan to June 2022.

Materials and Methods: Diagnosed Hyperthyroid Patients were selected and age ranging from 20 to 60 years for study purpose. Non probability convenience sampling was used and sample size was 100. Data was analyzed by using SPSS version 24.

Results: According to this study data mean age of the participants was 36.92 ± 7.47. Out of 100 participants who were diagnosed hyperthyroid patients, 43% were further diagnosed having Graves' disease. Graves' disease is 3 to 4 times high in females (74%) compared to males. Cardiovascular diseases (42%) are commonest comorbidities associated with hyperthyroidism.

Conclusion: This study concluded that Graves' disease is the more common cause of hyperthyroidism females are affected four times higher than male with Grave's disease in their 3rd to 5th decades of life in our public health care system. Comorbidities are very common in hyperthyroidism because of involvement of multiple organs and worsen the prognosis of the disease hence increase mortality.

Key Words: Graves, Disease, Hyperthyroid Patients, Associated Comorbidities

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INTRODUCTION

Hyperthyroidism also called hyper-active thyroid is a state in which the thyroid gland secretes enough amounts of free thyroid hormones. Thyroid gland produces two important hormones, Thyroxin (T4) and Tri-iodothyronine (T3) is a small, butterfly-shaped gland situated at lower anterior part of the neck.[1]

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These hormones T4 and T3 are regulated by Thyroid stimulating hormone (TSH), released from anterior pituitary gland in response to thyrotrophin releasing hormone (TRH) from hypothalamus[2]. Hormones secreted from the thyroid gland, have widespread actions over the body, they are major regulator of the body energy, metabolism and body development. Their actions includes regulating neurological, cardiovascular, musculoskeletal and reproductive functions[3,4].

Thyrotoxicosis a clinical state during which T4 and T3 levels are raised in blood, in which the thyroid hormone is toxic to tissues and produces specific clinical features[5]. Causes of high levels of thyroid hormones in blood are:

- Graves' disease
- Toxic multi-nodular goiter
- Thyroiditis
- External supplement of thyroid hormone
- Drugs (Amiodarone)
- Postpartum thyroiditis (PPT)
- Strumaovarii (Monodermal teratoma)
- Excess iodine consumption
- Pituitary adenoma[6,7].

Clinical presentation of hyperthyroidism: Main clinical signs are anxiety, weight loss, heat intolerance, hair loss (especially of the outer third of the eyebrows), muscle weakness, fatigue, hyperactivity, irritability, hyperglycemia, polyuria, delirium, polydipsia, tremor, pretibial myxedema (in Graves' disease), and perspiration[8]. Panic attacks, inability to concentrate, and memory problems may also occur. Psychosis and paranoia, common during thyroid storm, are rare with milder hyperthyroidism[9]. Addition to above symptoms, other symptoms may also present like palpitations, arrhythmias, dyspnea, loss of libido, amenorrhea, nausea, vomiting, diarrhea and feminization[10].

Graves' Disease: Among the causes of thyrotoxicosis, Graves' disease has significantly high prevalence. The data from western world suggest 60-80% prevalence of Graves' disease prevail among hyperthyroid patients worldwide. Female to male ratio of 7-10:1. Most cases reports from India described only 2-3 fold excess of female disease[11]. Graves' disease, autoimmune disorder of thyroid gland can either cause glandular destruction and hormone deficiencies called hypothyroidism or over production of thyroid hormone[12].

In Graves' disease forms the similar antibodies like TSH, which in turn causing the thyroid gland to secrete more thyroid hormone beyond the body requirements. This over production of TSH may result is overactive thyroid. An overactive thyroid can lead to speed up of all function of the body, like increase heartbeat, increase blood pressure and increase metabolism in turn produce energy. There are three types of auto antibodies identified for TSH receptor stimulation are:

1. TSI (Thyroid Stimulating Immunoglobulin):
2. Thyroid Growth Immunoglobulin (TGI):
3. Thyrotrophin Binding-Inhibiting Immunoglobulin (TBII):

Clinical presentation and lab tests to differentiate graves' disease from other causes of hyperthyroidism: Graves' disease can be diagnosed with a careful history and physical examination. Suggestive features of Graves' disease include a positive family history, the presence of orbitopathy, diffusely enlarged thyroid with or without bruit and pretibial myxedema[13]. Clinical manifestations of Graves' disease are:

- Exophthalmos (protrusion of eye)
- Pretibial myxedema
- Increase cardiac rate
- Weight loss, muscular fatigue, increased appetite etc,

Thyroid Function Test: Initially the primary test for the confirmation of hyperthyroidism is to measurement the level of TSH, secreted by the pituitary gland. A low level of TSH reveals that there is raised level of T_4 and/or T_3 in the blood.

Thyroid function test results in different causes of Hyperthyroidism

Sr. No.	Condition	TSH	T3/T4	TSI
1	Graves' disease	↓	↑	+
2	Thyroiditis (with hyperthyroidism)	↓	↑	−
3	Thyroid nodules (hot, or toxic)	↓	↑	−

Thyroid specific Antibody tests: Determine the level of anti-TSH-receptor antibodies in Graves' disease, or anti-thyroid-peroxidase in Hashimoto's thyroiditis, may also contribute in the diagnosis.

Thyroid scan: It is a peculiar test for the diagnosis of hyperthyroidism, and it differentiate it from thyroiditis.

Comorbidities associated with hyperthyroidism: Comorbidities, especially cardiovascular diseases, have most important influence on mortality. However, available studies are unpredictable when controlling for comorbidity. Some studies have highlighted the importance for control of cardiovascular diseases, some for diabetes, and some control for cancer.

A study concluded that hyperthyroidism is associated with a 21% increased risk in mortality due to all causes. The most common diseases explained in groups are myocardial infarction, heart failure, vascular disease, cerebrovascular disease, dementia, chronic lung disease, rheumatic disease, gastric ulcer, liver disease, diabetes mellitus with or without complications, hemiplegia, kidney disease, cancer, cancer with metastases, lymphoma, leukemia, liver failure, and AIDS[14].

Epidemiology: Graves' disease is the most common cause of Hyperthyroidism and affects nearly 0.5 percent of the population and is the under lying cause of 50-80 percent of all cases of hyperthyroidism.[15, 16]

In the United States, there is an estimate of 30 cases per 100,000 persons every year diagnosed to have Graves' disease. It is said to be the most prevalent autoimmune disease in the whole of America, having been diagnosed in 60-80% of patients with hyperthyroidism[17.]

Graves's disease is more common in women than it is with men and children. It has an annual incidence of 0.5 per 1000 of women, mostly affecting those in the 40 to 60 years old age bracket. Its prevalence rates are similar in Caucasians and Asians, but are lower in Africans[18].

In Pakistan the exact burden of this disease is not yet established. However limited studies were available as reported by Khan A et al in 2002, which showed that prevalence of hyperthyroidism and sub-clinical hyperthyroidism was 5.1% and 5.8% respectively[19] and was higher in females than males. Peak presentation occurs in the 3rd and 4th decades of life while the disease is rare in first decades and in the elderly[20].

MATERIALS AND METHODS

Study Setting: This descriptive Cross-Sectional study was conducted at Out Patient Department (OPD) of National Institute of Diabetes & Endocrinology (NIDE), Dow International Medical College Hospital (DIMC), and Medical Wards of Civil Hospital Karachi (CHK).

Sample Size was calculated using Open-Epi software, with 95% confidence interval and 5% margin of error. The calculated sample size was 100. Non-probability convenience sampling was used.

Inclusion criteria

1. Adults of both gender
2. Age between 20 to 60 years.
3. Diagnosed patients of Hyperthyroidism and all types of Goiter
4. Presence of either exophthalmos and / or pretibial myxedema.

Exclusion criteria

1. Age under 20 or over 60 years
2. History of Thyroid ablation or Thyroidectomy
3. Use of Centroids.
4. Excessive use of iodinated salts, drugs and sea foods.

Data Collection Procedure: After approval from Institutional Review Board, the diagnosed cases of Hyperthyroidism visited Out Patient Department (OPD) of National Institute of Diabetes & Endocrinology (NIDE), Dow International Medical College Hospital (DIMC), and Medical Wards of Civil Hospital Karachi (CHK), fulfilling the criteria were included in this study. After taking written consent the information were gathered on the pre-designed questionnaire for record. Demographic (age and sex) and clinical sign and symptom data were collected through structured questionnaire. Thyroid function test (TSH/ FT4/FT3), were done to confirm diagnosis.

Data Analysis Procedure: The data was analyzed in version 24 of the Statistical Package for Social Sciences (SPSS). For categorical variables, frequency and percentage were calculated. The data was formulated through Graphs and Charts.

RESULTS

Total hundred hyperthyroid patients were selected from Out Patient Department (OPD) of National Institute of Diabetes & Endocrinology (NIDE), Dow International Medical College Hospital (DIMC), and Medical Wards of Civil Hospital Karachi (CHK).

The table 1 shows that mean age of the participants was (36.92 ± 7.47). 48% percent participants were between 41 to 50 years of age, 25% were between 51 to 60 years, 21% were between 31 to 40 years only 06% participants were below 30 years of age. There was no or limited role of education in this disease majority of the subject were graduate (47%). 72% participants were from urban setting only 28% participants were from rural areas. Socioeconomic status was observed and majority of the participants were belonging to middle class (table 1).

Table No.1: Socio-demographic characteristics of Participants (n= 100)

Sr. No.	Characteristics	Category	Frequency	Percentage
1	Age of Participant (in years)	21-30	06	6%
		31-40	21	21%
		41-50	48	48%
		51-60	25	25%
2	Educational status	Primary	23	23%
		Secondary	30	30%
		Graduate	47	47%
3	Residence of Participants	Urban	72	(72%)
		Rural	28	(28%)
4	Socioeconomic Status of Participants	Lower Class	36	(36%)
		Middle Class	49	(49%)
		Upper Class	15	(15%)

Table No.2: 1. Gender distribution in hyperthyroid patients (n=100). 2. Gender distribution in Graves' disease (n=43)

Sr. No.	Characteristics	Category	Frequency	Percentage
1	Gender distribution of participants of hyperthyroid patients (n=100).	Male	31	(31%)
		Female	69	(69.0%)
2	Gender distribution of participants with Graves' Disease (n=43)	Male	11	(26%)
		Female	32	(74%)

Sr. No.01 of table 2 shows gender distribution in hyperthyroidism and is clearly evident in this study that is common female (69%) as compared to male (31%).
Se. No.02 shows gender distribution in Graves' disease, 31 (74%) out of total 43 were female and remaining 11 (26%) were male (table 2).

Figure No. 1: Percentage of Graves 'disease in Diagnosed hyperthyroid Patients (n=100)

The above graph shows the percentage of hyperthyroid patients who were diagnosed as Graves' disease. 43% participants were positive with Graves' disease and remaining 57 % were hyperthyroid but shown no signs of Graves' disease at the time of study.

Table No.3: Cardinal Clinical Signs and Symptoms of Graves' disease noticed in hyperthyroid patients (n=100)

Sr. No.	Clinical presentation	Frequency	Proportion
1	Exophthalmos / Opthalmoplagia (protrusion of eye)	34	34%
2	Pretibial myxedema	11	11%
3	Diffuse Goiter	47	47%
4	Palpitation (Increase cardiac rate)	74	74%
5	Weight loss, muscular fatigue, increased appetite etc.	82	82%

Figure No.2: Development of comorbidity in already diagnosed patients of hyperthyroidism (n=100)

The above chart shows pattern of comorbidities in hyperthyroid patients. It was seen in this study that cardiovascular diseases are (42%) and very common, diabetes was second common disease (12%) was noted. Other diseases like Chronic Lung disease were (8%), Hematological disorders were (8%) Chronic Renal failure were (4%) and others were (5%). 21% patients presented with no associated disease at the time of data collection.

DISCUSSION

In this study frequency of Graves' disease was observed in diagnosed hyperthyroid patients visiting in different tertiary care hospital of Karachi and it was concluded that 43% cases had findings of Graves' disease and it was the most common cause of hyperthyroidism. This is in accordance with the study conducted by Vanderpump et al which also show the same prevalence and frequency[11].

In this study Graves' disease was found four times higher in female than male. Female to male ratio was 4:1. Previous study also supported that Graves' disease is more common among female than male. Peak incidence of Graves' disease in current study was seen in middle age between third to fifth decades of life. Similar results were reported by a study conducted by Zimmerman MB et al in 2009[20].

Graves' disease can be diagnosed on the basis of cardinal clinical signs and elevated serum T4 and T3 levels present in hyperthyroid patients. Goiter with either exophthalmos and/ or pretibial myxedema are classical presentation of Graves' disease. In this study diffuse goiter was reported in (47%) patients with exophthalmos (34%) and pretibial myxedema (11%) cases. Palpitation was noted in (74%) and weight loss was very common and seen in (82%) cases. All 43 cases diagnosed as Graves' disease had common clinical presentation of palpitation, exophthalmos and weight loss. DeGroot LJ in his study pointed out similar signs and symptoms for the diagnosis of Graves' disease[21].

Comorbidities are very common in hyperthyroid patients because of involvement of almost all tissues and organs of the body. These comorbidities are associated with (21%) increased risk of mortality. The most common comorbidities recorded in our study were cardiovascular diseases (myocardial infarction, heart failure, vascular disease, cerebrovascular disease) 42%, second common disease was Diabetes (12%). Other diseases like chronic lung disease (8%), hematological disorders (8%) Chronic renal failure (4%) were noteworthy. A study conducted by Brandt F. et al also gave similar results in his study and ranked cardiovascular disease at top[14]. This study is in accordance with that study as well.

CONCLUSION

This study concluded that Graves' disease is the more common cause of hyperthyroidism females are affected four times higher than male with Grave's disease in their 3rd to 5th decades of life in our public health care

system. Comorbidities are very common in hyperthyroidism because of involvement of multiple organs and worsen the prognosis of the disease and increase mortality. Further studies are need to be conducted this study on larger scale with full diagnostic criteria.

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Original Article

Association of Papilledema with Headache Visualizing Via Smartphone Fundoscopy

Syed Maroof Ali, Fawwaz Bin Shahab, Aamir Saghir and Salman Sharif

ABSTRACT

Objective: To determine association of papilledema with headache using 20D lens and a smartphone for fundoscopy.

Study Design: Prospective Cross-sectional Study

Place and Duration of Study: This study was conducted at the Ophthalmology OPD at Liaqat National Hospital, Karachi from, 25th May 2022 till 25th July 2022.

Materials and Methods: Patients, presenting to ophthalmology OPD at Liaqat National Hospital, patient complaining of blurring of vision and difficulty focusing on distant object were included in our study. We used a 20D lens for indirect ophthalmoscopy and smartphone camera for recording and taking pictures. Participant's pupils were dilated using 1% tropicamide drops and waited for 15-20 mins for pupil dilation. Video recording was done with flashlight switched on and recording was reviewed for fundus pictures and snap shots were taken from it.

Results: 384 patients were included in the study. There were 65.6% male and 34.4% female patients in our study with mean age 41.93±13.50 years while majority (62.8%) were from age group >35 years. we found 3.6% of patients with obesity, 12.2% with diabetes mellitus, 14.3% with hypertension and 45.1% with headache and 7.3% of patients were found with papilledema. Strong association was found with papilledema and headache with p-value of <0.001.

Conclusion: Strong association of papilledema with headache was found in patients who came with symptoms of blurry vision and We can reliably do fundus visualization with Smartphone based indirect ophthalmoscopy to view optic disc for presence of papilledema, can be cheap alternative to conventional ophthalmoscopy devices even in neurosurgical examinations, in covid-19 era where social distancing is a norm and proximity to the patients with direct ophthalmoscopy can be discomforting in these circumstances.

Key Words: Indirect Ophthalmoscopy with Smartphone, Smartphone ophthalmoscopy, visualize papilledema with smartphones, smartphone fundoscopy, fundoscopy for neurosurgeons, headache with papilledema.

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INTRODUCTION

In Neurology and Neurosurgery, History and Examination plays a vital role in detecting and interpreting symptoms of the patients with multiple disorders. Fundoscopy is also a part of such examination but performing ophthalmoscopy is in decline in non-ophthalmic care givers due to technical difficulties, nevertheless it is still an important part of examination. The accreditation council for graduate medical education has emphasized the importance of fundoscopy and recommended to identify papilledema prior to independent practice.[1] Routine practice of fundoscopy is encouraged in hypertensive and stroke patients as it can helps in detection of papilledema and can help in diagnosing hypertensive encephalopathy thus obviating the need for urgent MRI.[2]

Fundoscopy via smartphone has become increasingly popular nowadays being inexpensive and its utility for rapid documentation. In the start the examination was done via lens held manually in optic path and images were captured with the help of smartphone. With increasing innovation, the development of smartphone adapters has made this examination much easier, now we can do both direct and indirect ophthalmoscopy using smartphones and its increasing applicability in lower resource settings. Another advantage of smartphone usage is its continuous online connectivity which can also help in telemedicine.[3] Ophthalmoscope used in current practice are derived from the design of early twentieth century and its applicability is limited due to its specialist skills, it's difficult for an untrained personnel and bare usage by practitioners. In low-income countries due to its high cost many centers

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failed to deliver its services where its strongly required.[4]

One such example of smartphone based fundoscopy is the use of D-EYE, it is a digital ophthalmoscope that attaches to the rear camera of the smart phone and acts as a direct ophthalmoscope, it can be used on both dilated and un-dilated pupil although the field of view will vary, in un-dilated pupil the field is around 5o to 8o and in dilated pupil it is around 20o, this device is used in conjunction with an HIPAA (Health insurance portability and accountability) compliant app and is approved by U.S. Food and Drug Administration.[5] Another example is that of indirect ophthalmoscope made by utilizing google cardboard, the smartphone is inserted in the google cardboard and another small acrylic lens is used in hand to do the indirect ophthalmoscopy, this is a very cheap alternative to conventional devices and it also allows for taking pictures and recording as well.[6] The use of smartphone based fundoscopy was applied on medical students as well and they find it relatively easy to learn compare to conventional devices, in the era of Covid-19 where maintaining social distancing and close proximity is avoided these devices can help overcome the obstacle of doing fundoscopy.[7]

In this study we will be only visualizing fundus to look for papilledema as there can be serious underlying cause for it. If the papilledema is present bilaterally it could be caused by IIH (idiopathic intracranial hypertension), obstructive hydrocephalus, cerebral venous sinus thrombosis or any underlying intracranial neoplasm, as papilledema is a sign of raised ICP urgent intervention is required to manage these conditions. Once damage is done it is not reversible and could lead to mortality and morbidity in patients.[8]

MATERIALS AND METHODS

This cross-sectional study was performed at Department of Ophthalmology, Liaquat National Hospital & Medical College, Karachi, Pakistan from 25th May 2022 till 25th July 2022 after getting the Ethical approval. Sample size was calculated using WHO calculator with 95% confidence and 5% margin of error resulting in sample size of 384 patients. Informed and written consent was taken from patients prior to their recruitment into the study through non-probability consecutive sampling technique. Only adults' patients from age 18 and above were included with symptoms of blurry vision and difficulty in focusing distant or near objects, any patient who has previous history of glaucoma, eye surgery and specification of lens were not included as it could hinder with examination.

We used an android smartphone and a 20D lens as shown in figure 1 for indirect ophthalmoscopy. Initially practiced on models and peers when comfortable then applied on patients as co-operation is necessary in this procedure. All the participants were neurosurgery residents, and they took turn on each other for examining the fundus of the eye. After getting comfortable with examining fundus on each other, we shifted towards examining the fundus of patients. We used 1% tropicamide drops for dilatation of the pupils and waited for 15-20 minutes for dilatation, patient should be on chair in front of you around 0.5 meter at the same level, tell the patient to look at the distant object. Start video recording in the smartphone with flashlight turned on. With another hand hold the 20 diopter (D) lens with your thumb and index finger and adjust it with your ring and little finger on patient's forehead and keep the eyelids opened. Hold the smartphone 10-40 cm away from the lens and gradually bring closer to the lens until you see the retina glow, adjust your camera until you see the fundus tilt a little to the lateral side as optic disc is present nasally, once done stop the recording and review and take snapshot of the fundus with good view.

Main concern of this project was to improve the quality of patient care and efficiency in health care system, the design used already established methods and did not have any physical or psychological burden on the participants. Informed and written consent were taken from all the patients before performing this procedure.

Statistical Analysis: Data analysis were performed by SPSS-v26. Mean and standard deviation was computed for quantitative variable while frequency and percentages were reported for qualitative variables. Association were checked by chi-square/fisher exact test. Odds were calculated by uni-variate and multivariate binary logistic regression. $P<0.05$ was considered as significant.

RESULTS

Total 384 patients with mean age 41.93±13.50 years were included in study. Detailed descriptive statistics of patient are presented in Table-1.

In our study, 7.3% of patients were found with papilledema. Table 2 shows comparison of patients' demographic and clinical features, showing significant difference among patients with papilledema from those without papilledema. No significant association was found with headache (p=0.000), gender (p=0.008), age (p=0.024), BMI (p=0.000) and diabetes mellitus as presented in Table-2.

Univariate binary logistic regression showed that male patients are less likely to have papilledema in comparison of female patients (OR=0.363, p=0.011). patients with age≤35 years are more likely to have papilledema in comparison to patients with age>35 years (OR=2.404, p=0.027) while diabetic patients are also found more likely to have papilledema in comparison to non-diabetic patients (OR=3.251, p=0.009). Detailed results of odds by Uni-Variate and multivariate binary logistic regression are presented in Table-3.

Table No.1: Descriptive statistics of study population (n=384)

	n (%)
Gender	
Male	252(65.6)
Female	132(34.4)
Age(years)	
Groups	
≤35 years	143(37.2)
>35 years	241(62.8)
BMI	
Underweight	11(2.9)
Normal	311(81)
Overweight	48(12.5)
Obese	14(3.6)
Diabetes Mellitus	
Yes	47(12.2)
No	337(87.8)
Hypertension	
Yes	55(14.3)
No	329(85.7)
Headache	
Yes	173(45.1)
No	211(54.9)
Papilledema	
Yes	28(7.3)
No	356(92.7)

SD; Standard Deviation

Table No.2: Association of Papilledema with demographics and co-morbid

	Papilledema n (%)		P-Value
	Yes	No	
Gender			
Male	12(42.9)	240(67.4)	0.008*
Female	16(57.1)	116(32.6)	
Age(years)			
≤35 years	16(57.1)	127(35.7)	0.024*
>35 years	12(42.9)	229(64.3)	
BMI			
Underweight	1(3.6)	10(2.8)	<0.001*
Normal	11(39.3)	300(84.3)	
Overweight	14(50)	34(9.6)	
Obese	2(7.1)	12(3.4)	
Diabetes Mellitus			
Yes	8(28.6)	39(11)	0.013*
No	20(71.4)	317(89)	
Hypertension			
Yes	4(14.3)	51(14.3)	1.000
No	24(85.7)	305(85.7)	
Headache			
Yes	3(10.7)	170(47.8)	<0.001*
No	25(89.3)	186(52.2)	

Chi-Square/Fisher exact test was applied.
P<0.05 considered as significant.
*Significant at 0.05.

Table No.3: Odds Ratio for Patients with Papilledema

	Un-Adjusted		Adjusted	
	P-Value	Odds Ratio(95% CI)	P-Value	Odds Ratio(95% CI)
Gender				
Male	0.011*	0.363(0.166-0.791)	0.004*	0.175(0.054-0.570)
Female®		1		1
Age(years)				
≤35 years	0.027*	2.404(1.103-5.241)	0.996	NA
>35 years®		1		1
BMI				
Underweight	0.694	0.600(0.047-7.630)		
Normal	0.066	0.220(0.044-1.104)		
Overweight	0.274	2.471(0.488-12.499)		
Obese®		1		
Diabetes Mellitus	0.009*	3.251(1.342-7.876)	0.123	2.604(0.773-8.778)
Yes		1		1
No®				
Hypertension				
Yes	0.995	0.997(0.332-2.992)		
No®		1		
Headache				
Yes	0.001	0.131(0.039-0.443)	0.996	<0.001(0.001-0.0009)
No®		1		1

®Reference group. Binary logistic regression was applied. P-value<0.05 considered as significant. *significant at 0.05 level.

DISCUSSION

Papilledema is defined as optic disc edema because of raised ICP. Papilledema can present with visual obscuration or blurring and be associated with headache in most cases. In. our study, prevalence of papilledema was found to be 7.3%, compared to an annual incidence of 2.5 individuals /100,000 in previous studies.[8]

Papilledema was found to be more common in females (57.1 v/s 42.9), was slightly more common in patients <35, compared with those >35 (57.1 v/s 42.9). There was no association noted between headache and papilledema in our study. As the cause of headache is mostly due to tension headache followed my migraine headache, papilledema will be less likely to be present in these patients.

A similar study was done by ophthalmology residents by applying 20 diopter lens and recording it via smartphone. Their results were comparable to indirect ophthalmoscopy, and they use this to train their residents on it.[9] Another study compares smartphone ophthalmoscopy with slit lamp bio microscopy to grade ventral cup-disc ratio in glaucoma patients. In this study a D-EYE adaptor was used to examine the optic disc in a patient without pupil dilation and their results were comparable to slit lamp examination. The limitation in their study was the examination were done by glaucoma specialist and more study would be required by to achieve its full potential in glaucoma examination.[10] One study utilizes the iPhone X for direct ophthalmoscopy using its telephoto lens for magnification. In this study pupils were dilated using 1% tropicamide and no adapter was involved in this study. The direct use of camera lens to take fundus images were employed but the field of view was limited to optic disc and its surrounding area nevertheless it was a good alternative for fundus imaging.[11]

Using the similar technique for indirect ophthalmoscopy using smartphones, retinopathy of prematurity was diagnosed in newborns, in their study they use a adaptor known as MII retcam, which is simply holding the smartphone and the 20D lens in one place so that the procedure can be done by only using one hand while the other can be used to stabilized the head and keep the open for examination. In addition to the pictures taken were sent teleophthalmology consultation as well, which makes a great tool for use in urban areas where such facilities are scarce.[12] In contrast to that one author has shared a 3D printable model of indirect ophthalmoscopy adaptor for smartphones, this adaptor attaches with the phone's back cover and a 20D lens is inserted on its other end. There is no extra equipment required and its pretty cheap to make via a 3D printer.[13] However in another article the author had made a smartphone adaptor using old sanitizer bottle and super glue while attaching the 20D lens on one side, a portable indirect ophthalmoscope was made which was very easy to operate and can give really good quality pictures.[14]

There are also some unconventional methods of doing indirect ophthalmoscopy using head mount lamp and a condenser lens 20D in one hand to visualize fundus by using this technique one can only visualize it but cannot record its findings, another method is the usage of nasal endoscope with contact method can give good view of fundus and the findings can be recorded as well.[15] All the above methods describe are good alternatives to conventional techniques of ophthalmoscopy, but they cannot replace the original devices. Our devices are not purposefully built for fundoscopy, and the original devices are too expensive to be utilized in every center of a developing country.

CONCLUSION

Strong association of papilledema with headache was found in patients who came with symptoms of blurry vision and Smartphone based fundoscopy can be used as an alternative to direct as well indirect ophthalmoscopy in neurosurgery setup to visualize fundus for papilledema, as they are significantly cheap these can be easily employed in out reached areas as well. In Covid-19 pandemic where social distancing is required and direct ophthalmoscopy is avoided because of its need for close proximity to the patient, in these situations' smartphone based fundoscopy can help avoid these obstacles in examination of papilledema. One more thing that can be applied is the use of Artificial Intelligence in interpreting the fundus photograph and can give instant results of normal or an abnormal fundus.

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Original Article

Pattern of Abnormal Uterine Bleeding and Spectrum of Endometrial Pathology Among Perimenopausal Women

Seema Ghani[1], Zubaida Masood[2], Humaira Tahir[3], Fauzia Ali[2], Shabnam Hassan[1] and Saira Saeed[4]

ABSTRACT

Objective: To determine the clinical pattern and endometrial pathology of abnormal uterine bleeding among perimenopausal women.

Study Design: Cross sectional study

Place and Duration of Study: This study was conducted at the Hamdard University Hospital, Karachi from July 2019 to December 2020.

Materials and Methods: 105 perimenopausal women between 40-50 years of age who presented with abnormal uterine bleeding (AUB), and underwent dilatation and curettage for endometrial sampling were enrolled in this study after informed consent. A detailed clinical assessment of patients performed in the outpatient department; included history and clinical examination. Patients' medical records were evaluated for parameters including age, parity, clinical presentation and ultrasound findings. Histopathology evaluation was done by histopathologists.

Results: 57.1% participants were of age between 40-45 years, and 58.1% women were Multiparous. Pattern of uterine bleeding in perimenopausal women about 66.7%, women had frequent menstrual cycle and prolonged duration of bleeding 78.1%, history of heavy bleeding with clots, in 22.9%, 5.7% and 14.3% women had complaint of inter-menstrual, premenstrual and breakthrough bleeding respectively. 59% patients had more than 18 mm endometrial thickness. Proliferative endometrium was the most prevalent diagnosis 39% followed by secretory endometrium 31.4%, hyperplasia without atypia 11.4%, polyp 10.5%, endometritis 2.9%, hyperplasia with atypia 2.9% and 1.9% patients diagnosed with cancer. Factors like parity, pattern of bleeding, US findings and endometrial thickness had significant impact on different types of histopathology (P-value<0.05).

Conclusion: This study emphasises the need of endometrial sampling as an important diagnostic tool that would help in individualising the management of abnormal uterine bleeding with a view to reduce unnecessary benign hysterectomy procedures.

Key Words: Abnormal uterine bleeding (AUB), Perimenopausal women, Ultrasound (U/S), endometrial histopathology, Dilatation and curettage.

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INTRODUCTION

The World Health Organization (WHO) defines the Perimenopause period as the 2–8 years period preceding menopause and one year following the last menstrual period. Following an increase in follicle stimulating hormone (FSH), the hormonal level (estrogen) is displaying an overall increase, which is distinguished by insufficiency of progesterone secretion[1]. Abnormal uterine bleeding (AUB) is defined as any variation from the normal menstrual cycle, including alterations in its regularity, frequency, heaviness of flow, duration of flow and the amount of blood loss. It is a very common gynaecological condition and one third of patients attending gynaecology OPD with this complaint.[2] AUB is an umbrella term which includes heavy menstrual bleeding, intermenstrual bleeding and ovulatory disorders which has replaced previously used inconsistent and confusing terminologies like menorrhagia, metrorrhagia and dysfunctional uterine bleeding[3-4]. International prevalence of AUB among women aged 15 to 49 years is believed to be between 3% and 30%, with a higher rate of occurrence around menarche and Perimenopause, and when irregular and intermenstrual bleeding are taken into consideration, the prevalence climbs to 35 percent or higher[5]. Atrophic

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endometrium, chronic endometritis, endometrial polyp, hyperplasia, and cancer are among the AUB pathologies that can be studied by histological evaluation of endometrial specimens obtained after dilatation and curettage in AUB cases[6]. There may be several structural or functional aetiologies for the AUB. The "International Federation of Gynaecology and Obstetrics" working group on menstrual disorders has developed a classification system (PALM–COEIN) for causes of the AUB. There are 9 main categories, which are arranged according to the acronym PALM–COEIN "polyp, adenomyosis, leiomyoma, malignancy, and hyperplasia – coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified". PALM side of the classification refers to structural causes that may be evaluated by imaging techniques and/or histopathology and the COEIN side by investigating the underlying medical disturbances[7]. Clinical bleeding patterns are determined by the heaviness, duration of flow, regularity, and frequency. The causes of AUB can either be structural (PALM) or non-structural (COEIN)[8].

MATERIALS AND METHODS

A cross sectional study was conducted in Hamdard University Hospital, Karachi from July 2019 to December 2020. This study was approved by ethics review committee of department of Obstetrics and Gynaecology. A Non-probability consecutive sampling technique was used. Sample size was obtained by using "Open Epi" sample size calculator taking statistics of Endometrial polyp in perimenopausal patients with AUB 10.4%[4], at margin of error 6% and confidence interval 95%. One hundred and five (n=105) perimenopausal women between 40-50 years of age who were presented with AUB which was defined as abnormal pattern of bleeding[4] in term of, volume of bleeding (heavy / normal/ light), regularity (Irregular/ regular/ absent), frequency (frequent/normal/ infrequent), duration (prolonged/ normal/shortened) and other such as "inter-menstrual, pre/post menstrual, breakthrough". All the women who were eligible on the basis of selection criteria enrolled. All the patients underwent dilatation and curettage (D & C) for endometrial sampling. Informed consents were also obtained prior to the procedure from all the participation. Patients below 40 years of age, postmenopausal women and women with other causes of abnormal uterine bleeding, coagulation disorders (thrombocytopenia, von willebrand's disease), Hypothyroidism, Liver diseases and those on Hormone therapy, and inadequate endometrial sample were excluded from the study. A detailed clinical assessment of patients performed in the outpatient department included history and gynaecological examination. Assessment of blood loss was done by passage of blood clots and number of pads used per day. Patients' medical records were reviewed to collect parameters including age, parity and clinical presentation. Ultrasound pelvis was done for the evaluation of endometrial thickness and for other structural causes of AUB. Endometrium was considered thickened or hyperplasic when endometrial thickness was ≥12 mm. Endometrial biopsies were performed in all the women and specimen saved in formalin. Microscopic evaluation was done by histopathologists. The spectrum of endometrial histopathology and structural causes as per the PALM component of FIGO classification system was studied.

Data was entered and analysed into SPSS version 22. Study variables like age, parity, pattern of bleeding, ultrasound findings and histopathology diagnosis were taken as a consideration. They were presented as frequency and percentages. Stratification for histopathology diagnosis was done with respect to all associated factors like parity, pattern of bleeding and ultrasound findings. Chi-square test was use for comparison and find out the association between study variables. Significance level kept 0.05.

RESULTS

In this study a total of 105 perimenopausal women were studied. Pattern of abnormal uterine bleeding and endometrial pathological spectrums were evaluated. The table 1 shows distribution of baseline characteristics and evaluation of the pattern of uterine bleeding. Majority 60(57.1%) of the participants were having age between 40-45 years with more than half 61(58.1%) of the women were Multiparous, 35(33.3%) women were grand Multiparous. Evaluation of the pattern of uterine bleeding in perimenopausal women revealed that 70(66.7%) women had frequent, 27(25.7%) had normal and only 8(7.6%) had history of infrequent menstrual cycle. Prolonged duration of bleeding was found in 70(66.7%) women, 31(29.5%) had normal and only 4(3.8%) women had shortened duration.82(78.1%) women had history of heavy bleeding with clots and 40(38.1%) women had irregular period.

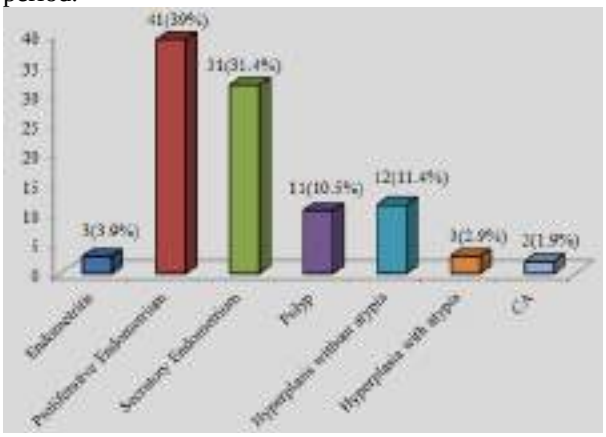

Figure No.1: Histopathological Diagnosis

Figure 1, presented the histopathology diagnosis distribution, Proliferative endometrium was observed among 39% of the perimenopausal women followed by secretory endometrium 31.4%, hyperplasia without atypia 11.4%, polyp 10.5%, endometritis 2.9%, hyperplasia diagnosed with atypia 2.9 and patients diagnosed with cancer 1.9%. We found that malignancy was least prevalent diagnosis.

Out of 105 study participants, 24(22.9%), 6(5.7%) and 15(14.3%) women had complaint of inter-menstrual, premenstrual and breakthrough bleeding respectively. Ultrasound findings showed that 18(17.1%) patients had adenomyosis, 16(15.2%) had fibroid, and polyp detect in 7(6.7%) patients. Among these women endometrial thickness was also assessed on Ultrasound findings showed that 62(59%) women had endometrial thickness more than 18 mm.

Table No.1: Patient's Baseline characteristics and Pattern of bleeding

Patient's Characteristics		**n (%)**
Age groups	40-45 years	60 (57.1%)
	46-50 years	45 (42.9%)
Parity	Nulliparous	9 (8.6%)
	Multipara 1-4	61 (58.1%)
	Grand multipara >4	35 (33.3%)
Characteristics of menstrual cycle		
Frequency	Frequent (<24 days)	70 (66.7%)
	Normal (24-38 days)	27 (25.7%)
	Infrequent(>38 days)	8 (7.6%)
Duration	Prolonged >8 days	70 (66.7%)
	Normal 4-8 days	31 (29.5%)
	Shortened <4 days	4 (3.8%)
Volume	Normal	23 (21.9%)
	Heavy with clots	82 (78.1%)
Regularity	Regular (2-20 days)	65 (61.9%)
	Irregular (>20 days)	40 (38.1%)
Inter-menstrual bleeding / spotting		24 (22.9%)
Premenstrual bleeding		6 (5.7%)
Breakthrough bleeding		15 (14.3%)
Endometrial thickness on ultrasound	Less than 18mm	43 (41%)
	18mm or more	62 (59%)
Ultrasound findings	Adenomyosis	18 (17.1%)
	Fibroid	16 (15.2%)
	Polyp	7 (6.7%)
	None	64(61%)

Comparisons of all histopathology diagnosis were done with the associated factors such as age of patients, parity, patterns of bleeding, ultrasound findings and endometrial thickness. Endometritis showed significant association with the duration of menstrual cycle (P= 0.019), Premenstrual bleeding (P= 0.037), and endometrial thickness (P= 0.035). Proliferative Endometrium showed significant association with the frequency of menstrual cycle (P= 0.000), Intermenstrual bleeding/spotting (P= 0.002), Postmenstrual bleeding (P= 0.047), and Ultrasound findings (P= 0.008). Secretory Endometrium showed significant association with the Parity (P= 0.000), Regularity of menstrual cycle (P= 0.048), Duration of menstrual cycle (P= 0.009), Intermenstrual bleeding/spotting (P= 0.005), Breakthrough bleeding (P= 0.033), and Ultrasound findings (P= 0.000), and endometrial thickness (P= 0.006). Polyp showed significant association with the Duration of menstrual cycle (P= 0.046), Intermenstrual bleeding/spotting (P= 0.000), Premenstrual bleeding/spotting (P= 0.001), Breakthrough bleeding (P= 0.002), Ultrasound findings (P= 0.000), and endometrial thickness (P= 0.003). Hyperplasia without atypia showed significant association with the parity (P= 0.042), and endometrial thickness (P= 0.025). Hyperplasia with atypia showed significant association with the regularity of menstrual cycle (P= 0.025) (Table-2)

Table No.2: Comparison of Histopathology findings with associated factors

Study variables		Common Histopathological Diagnosis						
		Endometritis	Proliferative endometrium	Secretory endometrium	Polyp	Hyperplasia without atypia	Hyperplasia with atypia	Carci-noma
Parity	Nulliparous	0(0%)	1(11.1%)	8(88.9%)	0(0%)	0(0%)	0(0%)	0(0%)
	Multipara 1-4	3(4.9%)	25(41%)	12(19.7%)	9(14.8%)	11(18%)	1(1.6%)	0(0%)
	Grandpara> 4	0(0%)	15(42.9%)	13(37.1%)	2(5.7%)	1(2.9%)	2(5.7%)	2(5.7%)
P-values		0.328**	0.196**	**0.000***	0.213**	**0.042***	0.445**	0.130**
Frequency of menstrual cycle	<24 days	1(1.4%)	33(47.1%)	20(28.6%)	7(10%)	6(8.6%)	3(4.3%)	0(0%)
	24-38 days	2(7.4%)	2(7.4%)	12(44.4%)	4(14.8%)	6(22.2%)	0(0%)	1(3.7%)
	>38 days	0(0%)	6(75%)	1(12.5%)	0(0%)	0(0%)	0(0%)	1(12.5%)
P-values		0.251**	**0.000***	0.156**	0.474**	0.095**	0.462**	**0.036***
Duration of menstrual cycle	Prolonged	2(2.9%)	29(41.4%)	17(24.3%)	11(15.7%)	8(11.4%)	1(1.4%)	2(2.9%)
	Normal	0(0%)	10(32.3%)	16(51.6%)	0(0%)	3(7.9%)	2(6.5%)	0(0%)
	Shortened	1(25%)	2(50%)	0(0%)	0(0%)	1(25%)	0(0%)	0(0%)
P-values		**0.019***	0.616**	**0.009***	**0.046***	0.663**	0.354**	0.601**
Regularity of menstrual cycle	Regular	2(3.1%)	23(35.4%)	25(38.5%)	6(9.2%)	8(12.3%)	0(0%)	1(1.5%)
	Irregular	1(2.5%)	18(45%)	8(20%)	5(12.5%)	4(10%)	3(7.5%)	1(2.5%)
P-values		0.863**	0.327**	**0.048***	0.745**	0.718**	**0.025***	0.726**
Intermenstrual bleeding/spotting	Yes	0(0%)	3(12.5%)	2(8.3%)	11(45.8%)	4(16.7%)	2(8.3%)	2(8.3%)
	No	3(3.7%)	38(46.9%)	31(38.3%)	0(0%)	8(9.9%)	1(1.2%)	0(0%)
P-values		0.339**	**0.002***	**0.005***	**0.000***	0.358**	0.130**	0.051**
Premenstrual bleeding	Yes	1(16.7%)	0(0%)	0(0%)	3(50%)	1(16.7%)	0(0%)	1(16.7%)
	No	2(2%)	41(41.4%)	33(33.3%)	8(8.1%)	11(11.1%)	3(3%)	1(1%)

DISCUSSION

AUB is a variation from normal menstruation which consists of abnormal frequency, lasting excessively long, irregular, and heavier than normal is potentially a serious condition as excessive bleeding causes anaemia and affect quality of life leading to unnecessary hysterectomy.

Our study recruited one hundred and five endometrial samples of perimenopausal women with abnormal uterine bleeding. We observed that the age of the majority of the participants (57.1%) ranged between 40-45 years. Most prevalent bleeding pattern was heavy bleeding with clots (78%), frequent cycle and prolonged duration of bleeding (66.7%). Among our samples, we observed that majority of the women were multiparous (58.1%). In accordance with the observation of the following studies that AUB was common 32%[4], 31%[9], 33.5%[10] and 37%[11] in age group 41-50years respectively. The difference in percentages is due to various age groups studied whereas in the present study women of age 41-50 years were included[12], whereas Indrani M et al observed 57.4% women presented with AUB in 40-44 years age group[1,9, 13].

The pattern of uterine bleeding in our study showed that 66.7%women had frequent menstrual cycle, 66.7% had prolonged duration, 78.1% had heavy flow with clot, 22.9% women had complaint of inter-menstrual bleeding, and other showed that prolonged bleeding was the most prevalent AUB found in 42% patients, followed by heavy 35%, frequent 20% and 19% had intermenstrual bleeding[8].

AUB in perimenopausal and postmenopausal patients is alarming and needs meticulous evaluation because it could be the only clinical symptom of endometrial carcinoma and pre-neoplastic conditions in these patients. We assessed patterns in ultrasound and histopathological findings. In this series we observed that most of the women (59%) presented with more than 18mm thickened endometrium and 41% women had less than 18 mm in ultrasound, while another showed 23% fibroid, 7.7% adenomyosis, 4.7% polyp, thickened endometrium 4% and 58% normal scan findings[12]. The study conducted in Kenya[8] demonstrated 31% fibroid, 7% adenomyosis, 6% polyp and thickened endometrium10%.

In our study proliferative endometrium was found as the most prevalent histopathological finding observed among 39% women followed by secretory endometrium which was found in 31.4% subjects whereas malignancy (1.9%), endometritis (3.9%) and hyperplasia with atypia (2.9%) were least prevalent findings of endometrial histopathology and others [9, 14] that showed proliferative endometrium as most common finding. A study conducted in 2020 in Pakistan, a endometrial polyps were identified in 15% of patients, endometrial hyperplasia in 12.5%, aberrant proliferative of endometrium in 8.3% of cases and cancer in 2.5% was discovered[11]. Moreover, proliferative phase endometrium was the most common histopathological pattern, found in almost 1/3rd of cases, followed by endometrial hyperplasia 24.8%, chronic endometritis 16.8%, secretory phase 16.8%, and endometrial polyps 4.2%[15]. The results of present study also correspond with another study from Pakistan, where on analysing the histopathology results of the samples 34% were showing proliferative endometrium[16]. Similarly in another study the most

common histological pattern of endometrium includes proliferative endometrium (22.8%) followed by endometrial hyperplasia (19.40%) [17]. On the contrary, secretory endometrium revealed in 38.88% cases, proliferative endometrium in 34.92%, endometritis 7%, atypical hyperplasia 3.1% and carcinoma endometrium in 5.55% cases[18,19]. In a study done in Nigeria, endometritis prevailed 25%followed by atypical hyperplasia 50% while typical Hyperplasia 31.7%, endometrial polyps 43.8% respectively [20]. Our study finding with regards to histopathology is variable. This could be because of difference in sample size, and study design. Break through, Intermenstrual and premenstrual bleeding had significant association with polyp, and endometritis. Ultrasound findings had significant association with polyp, Proliferative and secretory endometrium, and endometrium thickness had significant association with endometritis, secretary endometrium, polyp, hyperplasia without atypia.

CONCLUSION

Dilatation and curettage is a cost-effective procedure in the evaluation of abnormal uterine bleeding. Accurate analysis of endometrial sampling is the key to effective therapy and optimal outcome. This would help in individualising the management of abnormal uterine bleeding with a view to reduce unnecessary benign hysterectomy.

Author's Contribution:

Concept & Design of Study:	Seema Ghani, Zubaida Masood
Drafting:	Humaira Tahir, Fauzia Ali
Data Analysis:	Shabnam Hassan, Saira Saeed
Revisiting Critically:	Seema Ghani, Zubaida Masood
Final Approval of version:	Seema Ghani, Zubaida Masood, Saira Saeed

Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

The Demographic Characteristics and Level of Physical Activity in Patients Presenting with Heart Diseases at a Tertiary Care Center

Ahmed Ali Khan[1], Aisha Qamar[2], Syed Muhammad Ishaque[3], Abdullah Jan Panezai[4], Samia Khalid[2] and Nasim Marvi[2]

ABSTRACT

Objective: To determine the demographic characteristics and level of physical activity in patients presenting with heart-related complaints and heart diseases at a tertiary care hospital in Karachi.

Study Design: Cross-Sectional Study

Place and Duration of Study: This study was conducted at the PNS Shifa Hospital, Karachi from January 2021 to July 2021.

Materials and Methods: The participants were in-patients enrolled after informed consent. The data was acquired using patient evaluation proforma. The continuous variables were expressed as mean and standard deviation, and the categorical variables were expressed as frequency and percentages. Physical activity level was categorized as a daily walk of more than 30 minutes, 30 minutes or less and infrequent.

Results: Out of 79 adult patients, 44 (55.7%) were males and 35 (44.3%) females. There were 35 (44.3%) participants who had comorbidities, the most common being diabetes mellitus and hypertension. Of the 23 (29.1%) participants who had an addiction, 11 (13.9%) took smokeless tobacco and 06 (7.6%) were smokers. Most participants had no formal education [47 (59.5%)]. The occupation profile showed that 36 (45.6%) participants were housewives and 17 (21.5%) retired persons. A large number of participants had infrequent physical activity [48 (60.8%)], which was observed more in females [28 (35.4%)].

Conclusion: Females are more at risk of developing heart diseases due to sedentary life styles and low education, developing disease at an earlier mean age compared to males.

Key Words: Body mass index (BMI), Body surface area (BSA), Cardiovascular disease, Demographic characteristics, Physical activity level, Sedentary lifestyle

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INTRODUCTION

Heart diseases are considered an epidemic of the late 20th century that has persisted into the 21stcentury.[1,2] It has been predicted in the past that people dying from cardiovascular diseases will reach pandemic proportion by the year 2020.[3]

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Cardiovascular diseases are a spectrum of disorders that refer collectively to diseases of the heart and blood vessels. Heart diseases may be congenital in origin or acquired later in life. The latter category has gained focus due to its high prevalence and morbidity, and the treatment costs associated with it. Despite advances in early diagnosis and better treatment options available today, cardiovascular diseases remain the leading cause of death worldwide and a major cause of disability.[4] Focusing on modifiable risk factors will allow prevention of developing cardiovascular diseases through therapeutic and preventive measures.[5]

Modifiable risk factors are subject to vary regionally, due to differences that are pertinent to geography and life styles influenced by local cultures. Even within a country, the geographical profiles of cardiovascular disease risk factors vary.[6] This necessitates local studies investigating the demographic characteristics of indigenous and non-indigenous populations to determine the factors that render them susceptible to developing these diseases.

When gender is considered, females are generally thought to be protected from developing cardiovascular diseases. They develop disease 7-10 years later compared to males but have a higher prevalence, which makes it a major cause of death in females.[7] A trend of decreasing age at diagnosis for cardiovascular diseases and their risk factors has been observed among females in the United States (US), which highlights the need for prevention earlier in life and mandates gender-specific interventions.[8] Comorbidities further increase the problem, as they differ based on gender and the geographical region. The risk factors for some conditions are similar, e.g. diabetes mellitus and hypertension, and there is a substantial overlap in the cardiovascular complications that follow.[9] Moreover, both genders respond to risk factors differently.

Community-based awareness programs focus on the avoidance of risk factors and to promote physical activities.[10] Sparing time for regular physical activity is not a priority especially in the developing countries, which can be attributed to poverty, occupation, stress, lack of knowledge and facilities e.g. public parks, gymnasiums and fitness clubs. The physical activity guidelines for Americans[11] recommend that adults should get at least 150 minutes per week of moderate-intensity aerobic activity (e.g. walking), or 75 minutes per week of vigorous-intensity aerobic activity (e.g. jogging), or a combination of both. Muscle strength training activities are also recommended on two or more days per week.[12]

Educational institutions play an important role in the awareness about preventable diseases at an early age.[13] Countries with poor education set up, or low school-going population, are deprived of such merits. Although access to education and information is more available today, the aged population presenting with cardiovascular diseases did not have such luxury 30 years ago.

MATERIALS AND METHODS

It was a cross-sectional study, conducted in the Department of Cardiology at PNS Shifa Hospital, Karachi from January to July 2021, after approval by the ethical review committee (ERC) of Bahria University Medical and Dental College (BUMDC), Karachi. The sample size was calculated using the OpenEpi open-source calculator. All participants were in-patients admitted with signs and symptoms or complaints related to heart diseases. Those who met the inclusion criteria were selected through consecutive nonprobability sampling and enrolled after informed consent. The data was acquired using patient evaluation proforma and analyzed using SPSS (version 23). The height and weight of the participants were measured using a column scale with an integrated stadiometer. The BMI was calculated using the equation: Weight (kg)/ [Height (m)] ^{2}. The BSA was calculated using the DuBois & DuBois formula: 0.007184 x Weight (kg) $^{0.425}$ x Height (cm) $^{0.725}$. Physical activity level was analyzed using chi-square test and categorized as a daily walk of more than 30 minutes, 30 minutes or less and infrequent. For analysis, the participants were categorized in different age groups, based on age range with a class interval of 10 years. The continuous variables (ages, height, weight, BMI and BSA) were expressed as mean and standard deviation, and the categorical variables (gender, ethnicity, education, occupation, addictions and physical activity) were expressed as frequency and percentages. A probability (p) value of < 0.05 was considered statistically significant (and < 0.01, highly significant).

RESULTS

Of the total 79 patients with a mean age of 52.71±14.54 years (ranging from 19 to 75 years), 44 (55.7%) were males with a mean age of 55.11±14.34, and 35 (44.3%) females with a mean age of 49.69±14.42. The mean weight, height and BMI of the total study population were 65.54 kg, 1.61 m (161 cm) and 25.54 kg/m^2 respectively. The mean values for the same in males were 69.27 kg, 1.67 m (167 cm), and 24.98 kg/m^2 respectively, and in females were 60.86 kg, 1.54 m (154 cm), and 26.03 kg/m^2 respectively. The BSA was 1.69 m^2 for the total study population, 1.77 m^2 for males and 1.58 m^2 for females. The mean values of height, weight, BMI and BSA were compared between male and female participants using one-way ANOVA, and the results showed a highly significant difference (p-value < 0.001).

According to age, most participants belonged to the 61 to 70 years (29.1%) age group, followed by 51 to 60 years (25.3%) age group, and the least number were observed in the 21 to 30 years (3.8%) age group. The gender distribution in each of the age groups is shown in Table-1. The ethnic groups included 26 (32.9%) Urdu Speaking, 22 (27.9%) Pashtun, 18 (22.8%) Sindhi, 09 (11.4%) Baloch, 02 (2.5%) Punjabi and 02 (2.5%) Saraiki participants. The gender distribution in each ethnic group is shown in Figure-1.

The education level of the male and female participants is shown in Figure-2. Of the total participants, 47 (59.5%) had no formal education, 16 (20.3%) had matriculated, 11 (13.9%) primary education, 02 (2.5%) had intermediate or higher secondary education, 02 (2.5%) had madrasah education, and 01 (1.3%) had graduation. The occupation profile of the participants is shown in Figure-3, and the addiction profile is shown in Figure-4. The addictions in male and female participants are shown in Figure-5.

The physical activity level in both male and female participants, along with level of significance, is shown in Table-2. The comorbidities observed in the participants are shown in Figure-6. Diabetes mellitus and hypertension was observed in 12 (15.2%) males and 10 (12.7%) females. Hypertension was observed in 03 (3.8%) males and 06 (7.6%) females.

Table-1: Physical characteristics of the total study participants

Age Groups	Gender (n (%))		Weight (kg)		Height (cm)		BMI (kg/m^2)		BSA (m^2)	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
≤ 20	3(6.8%)	1(2.9%)	68.00	55.00	170.18	152.40	23.45	23.68	1.77	1.90
21 - 30	0(0.0%)	3(8.5%)	-	56.00	-	157.48	-	22.60	-	1.63
31 - 40	4(9.1%)	6(17.1%)	64.00	62.67	161.92	151.55	24.29	27.29	1.61	1.71
41 - 50	7(15.9%)	7(20.0%)	67.86	62.71	161.47	155.66	26.00	25.95	1.64	1.67
51 - 60	11(25.0%)	9(25.7%)	69.82	63.67	163.02	156.97	26.28	25.88	1.72	1.74
61 - 70	15(34.1%)	8(22.9%)	71.00	61.75	168.14	152.72	25.21	26.55	1.67	1.70
≥ 71	4(9.1%)	1(2.9%)	63.00	53.00	172.08	142.22	21.37	26.20	1.65	1.59

Table No.2: Physical activity level and its significance

		Gender		Total	p-value
		Male	Female		
Activity Level	Walk > 30 min	08 (10.1%)	03 (3.8%)	11 (13.9%)	0.007*
	Walk ≤ 30 min	16 (20.3%)	04 (5.1%)	20 (25.3%)	
	Infrequent	20 (25.3%)	28 (35.4%)	48 (60.8%)	
Total		44 (55.7%)	35 (44.3%)	79 (100.0%)	

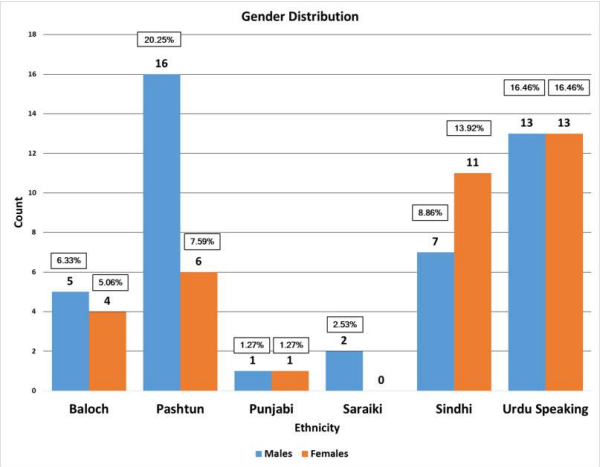

Figure No.1: Ethnic profile and gender distribution of the total study participants

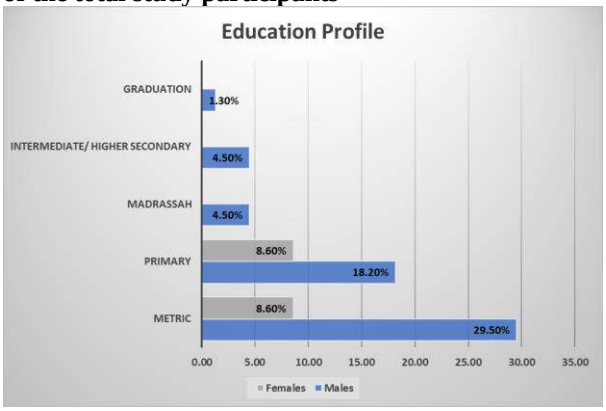

Figure No.2: Education profile of the male and female participants

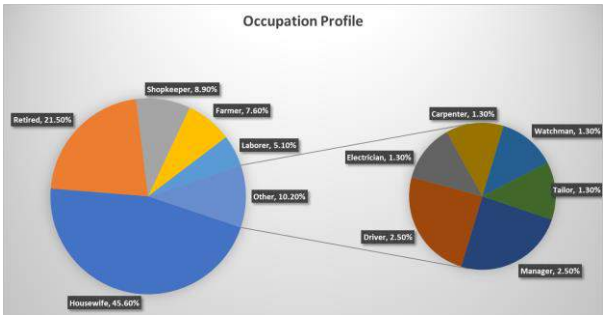

Figure No.3: Occupation profile of the total study participants

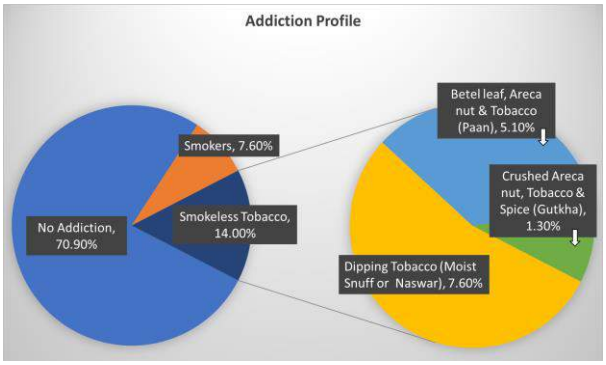

Figure No.4: Addiction profile of the total study participants

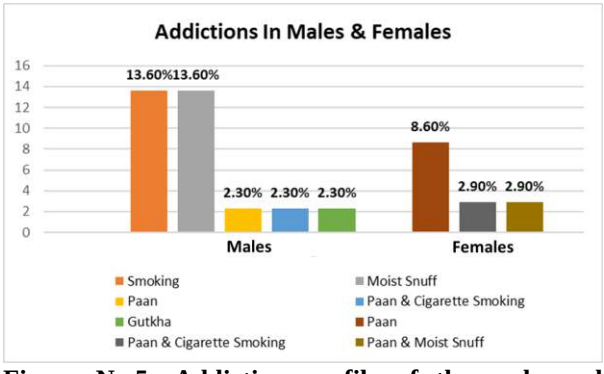

Figure No.5: Addiction profile of the male and female participants

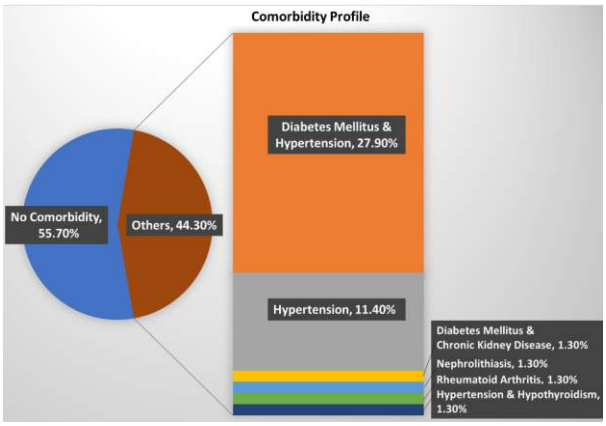

Figure No.6: Comorbidity profile of the total study participants

DISCUSSION

The demographic characteristics in our study were comparable to the findings of other studies conducted in our geographical region. When compared to an Indian study,[14] the mean heights of male and female participants were similar but the mean weights in our study were significantly higher for both genders. In an Iranian study,[15] the mean height of males and the weights of males and females were similar to our observation, but the mean height of females in our study was smaller. The maximum age of participants in the Indian study was smaller than the Iranian study, and smaller in both when compared to our study.

The BMI of both genders in our study were greater than the Indian study but similar to the values observed in the Iranian study. These differences are most probably due to our study comprising of diseased persons, most of them being overweight, while the Indian study included healthy participants and the Iranian study included both healthy and overweight. In all these studies, the females had a higher BMI compared to males. In our study, this difference can be attributed to the greater mean height of male participants. Compared to our study, a study[16] in Multan, Pakistan with a mean age of the participants half that observed in our study, reported smaller mean BSA values for both genders. Another study[17] in Karachi, Pakistan with a mean age of the participants smaller than that observed in our study, reported higher mean values for BSA, height and weight but similar BMI values for the total study participants. These differences reflect the influence of age on BSA, which is known to depend on more than just weight and height.

The male participants dominated older age groups in our study, which compares favourably to a study[8] that reported males in the US had an increased incidence of cardiovascular disease with increasing age while females had an increased incidence of stroke. A study[18] has reported an increased prevalence of cardiovascular disease in middle-aged females, although the age at which they present was reported to be older compared to males.

A study[19] has reported an ethnic distribution similar to our study, in which the most numerous study participants in descending order were Urdu Speaking, Pashtuns, and Sindhis. The study also reported Sindhis to have the least risk of 10 years atherosclerotic cardiovascular events, while the Urdu Speaking had the highest risk. Another study[20] also reported a higher risk of atherosclerotic cardiovascular disease in the Urdu Speaking, followed by Punjabis and Pashtuns. We observed a significantly large number of males belonged to the Pashtun ethnicity. A study[21] investigating gender and ethnic differences regarding prevalence of obesity and the risk factors for cardiovascular disease among indigenous and migrant communities reported a high prevalence of obesity in females and a higher prevalence of risk factors for cardiovascular disease in Urdu Speaking and Balochs.

We observed a lower education level to be associated with an increased incidence in heart diseases, which compares favourably to a study[22] that reported a reduced incidence of cardiovascular diseases in subjects with university education when compared to those with primary or lower education. In contrast, a study[8] in the US reported most participants with cardiovascular disease had a high school education, followed by a college or higher education.

Occupation contributes in the development of cardiovascular disease, and it is influenced profoundly by the cultural norms and education level. Most participants in our study were housewives, followed by retired persons, shopkeepers and farmers. Unique ageing physiology with hormonal changes and as housewives with infrequent physical activity, predisposes females to developing cardiovascular disease.[23] Findings reported by previous studies[24,25] state that physical activity level of retired persons influence the outcome for developing cardiovascular disease. Our study also identified farmers to be a vulnerable population for developing heart diseases, who are generally expected to have a healthier diet and physically active lifestyle, and thus protected from cardiovascular disease. It is attributed to abandoning traditional methods of farming and adapting urban diets.[26] The physical activity level in our study showed that females had a less physically active lifestyle compared to males, who had a moderate physical activity. The findings of our study are consistent with a study[27] that reported sedentary behavior increased the risk of cardiovascular disease.

Both diabetes mellitus and hypertension share common underlying risk factors and complications, comparing favourably to our observation[28]. Since the study population comprised of diseased persons, most participants did not have any addictions. The total number of smokeless tobacco users was higher

compared to cigarette smokers. A study[29] reported that although all tobacco products are hazardous and have a risk for serious disease, smokeless tobacco users in the US had a significantly lower mortality risk compared to exclusive cigarette smokers. But the types of smokeless tobacco available in subcontinent are different and include substances derived from areca nut, known to be responsible for a high frequency of oral cancers among users.[30]

CONCLUSION

The demographic characteristics of patients can help identify the vulnerable among the population and serve as a surveillance tool for risk factors of non-communicable diseases. Females are more at risk of developing heart diseases due to a sedentary lifestyle and low education. They develop the disease at an earlier age compared to males. Having a moderate physical activity level, males developed heart diseases at a later age. Urdu Speaking ethnic group exhibit a high prevalence of heart diseases.

Recommendation: Multicenter studies at the provincial level, with a larger sample size, are required to investigate the true magnitude of the effect resulting from demographic differences, including ethnicity.

Author's Contribution:

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Drafting:	Syed Muhammad Ishaque, Abdullah Jan Panezai
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Revisiting Critically:	Ahmed Ali Khan, Aisha Qamar
Final Approval of version:	Ahmed Ali Khan, Aisha Qamar

Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Morphometric Study of Mobile Phone Induced Injury to Cerebellum with Preventive Effects of Ginger in Albino Rats

Syed Alamdar Raza Zaidi[1], Shabnam Khan[2], Nasim Marvi[2], Ashia Qamar[3], Meesum Iftakair[2] and Samia Khalid[3]

ABSTRACT

Objective: To observe the effects of radio frequency (RF) radiation generated by third generation (3G) mobile phones on the rat cerebellum and possible protection provided by ginger in alleviating this injury in albino rats.

Study Design: Prospective Experimental Study

Place and Duration of Study: This study was conducted at the Basic Medical Sciences Institute (BMSI), Jinnah postgraduate Medical Centre (JPMC) for 6 months from January 2021 to July 2021.

Materials and Methods: Twenty four adult rats were procured from the animal unit of BMSI and arranged into four groups according to the assigned treatment. Group A: control; group B: 2100MHz RF radiation generated by 3G mobile phone; Group C: RF radiation and oral ginger 250mg/kg/day and Group D: ginger only. The rats were euthanized at termination of study. Brain of rats was processed for H & E stain to record thickness of granular layer as well as diameter of Purkinje fibers and Beilschowsky stain to observe microscopic anatomy of cerebellum.

Results: There was highly significant decrease in thickness of granular layer and decreased diameter of Purkinje neurons in RF radiation treated rats in group B as compared to controls. Distortion in the morphology of Purkinje cells and decreased number of axons were observed in tissue sections from group B animals as compared to control. These findings improved to a pronounced extent in group C animals who were given ginger concomitant to RF radiation by mobile phones.

Conclusion: The cerebellum of rat brain is sensitive to damage by radiofrequency radiations emitted by cell phones. However, ginger minimizes these damaging effects when used simultaneously.

Key Words: Radiofrequency radiation, Brain, Cerebellum, Ginger, Microscopic Anatomy

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INTRODUCTION

Brain is an indispensable organ of human body, comprising of nervous tissue enclosed in skull. It processes not only sensory input, but also controls vital functions such as regulation of blood pressure and respiration, motor activity and release of hormones. Thus damage to this organ results in disruption of all vital functions of human body.

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Damage to the brain can take place due to different conditions, diseases or injury, which includes poisoning, extended shortage of oxygen, physical trauma, infection, and oxidative stress[1].

There has been rapid growth in cell phone industry worldwide[2]. They operate at frequencies from 450 to 2700 MHz, which is included in radiofrequency field of non-ionizing radiation[3,4]**.** The radiofrequency radiation causes vibration of polar or charged molecules in the human body because of penetration of cells leading to thermal as well as non-thermal stress. This shows that exposure to radiofrequency radiation is hazardous for human health**,** especially brain[6]. Research has revealed that these injurious effects are caused by release of reactive oxygen species (ROS), which results in oxidative stress and lipid peroxidation, having a critical function in disease pathogenesis[1,7].

The use of medicinal plants as remedy for illnesses has increased over the past several years, especially because of their anti-oxidant effects[8]. Numerous studies have been carried out on Ginger as it defends against oxidative stress. Ginger (Z. officinale Roscoe) is an ancient herb[9]. It has different medicinal attributes like antioxidant, immunomodulatory, anti- hyperglycemic, anti-inflammatory, anti-apoptotic, anti- tumorigenic,

anti- lipidemic, hepatoprotective and neuroprotective activities[10].

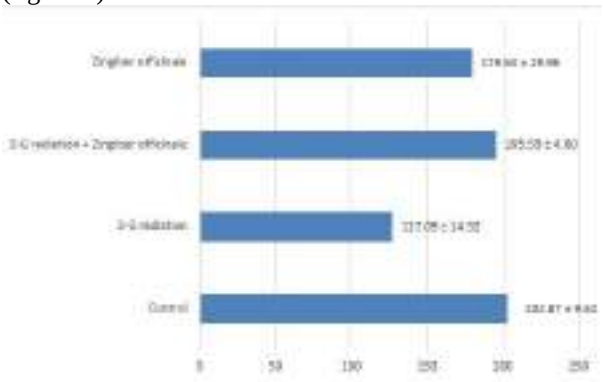
Many studies have shown that excessive use of mobile phones has harmful effects on brain, as the source emitting electromagnetic radiation is placed near to the user's head. These results may result in penetration of electromagnetic radiation into the human brain, causing damage[11]. With these facts in consideration, the present study was planned to analyze the damaging effects of electromagnetic radiation generated by 3G mobile phone on the cerebellum of rat, and prospective improvement provided by concurrent consumption of ginger by the albino rats.

MATERIALS AND METHODS

This study was undertaken at department of Anatomy, BMSI, JPMC, Karachi after securing ethical approval from the ethical review committee of JPMC. Twenty four adult albino rats of both sexes were acquired from the animal house. The rats were evaluated for one week before beginning of the study for their health by observing their diet intake and activity. The animals were sorted into groups based on treatment administered. Each group consisted of six animals. Group A: control, Group B: 2100MHz radiation generated by 3G mobile phone round the clock daily; Group C: dosage of radiation similar to group B with daily oral ginger 250mg/kg body weight; Group D: same dosage of ginger as administered to group C. The animals were allotted numbers and placed in plastic containers under laboratory conditions. Animals were irradiated with 2100MHz radiation generated by 3G mobile phones by hanging the phone 4-5cm from the floor of container with wire (Telenor Easy 3G, Model: W2). The animals were sacrificed at the end of study by administering ether anaesthesia in a glass jar. They were then fixed to an autopsy board. Parietal approach was used to remove brain, which was washed with normal saline and fixed by immersing in formal saline (10%) for a day. Then a small piece (about 2mm square) was sliced from the superior surface of cerebellar hemisphere and processed for making paraffin blocks for Haematoxylin and eosin and Bielschowsky stain[12]. Tissue block was fixed in a rotary microtome and 4 micron thick sections were made. The ribbons of tissue sections were soaked at 42° C in water bath and taken up on marked glass slides. Staining of cerebellar tissue was undertaken with Haematoxylin and eosin stain[12] for morphometry (measuring thickness of granular layer and diameter of Purkinje cells) and with Beilschowsky stain (Bancroft) to assess histological structure of axons and Purkinje cells at high magnification. Morphometry was done by calibrating ocular reticule with stage micrometer using 100 X objective. 50 small divisions of ocular micrometer coincided with 5 divisions of stage micrometer, which were equal to 50 µm, so one small division of ocular micrometer was equal to 1 µm at 100X objective. Quantitative data that is thickness of granular layer and diameter of Purkinje neurons were analyzed with SPSS software, version 21. The differences between the irradiated and control groups were analyzed by paired sample student "t" test. The difference between the groups was regarded significant statistically if p-value was equal to or less than 0.05.

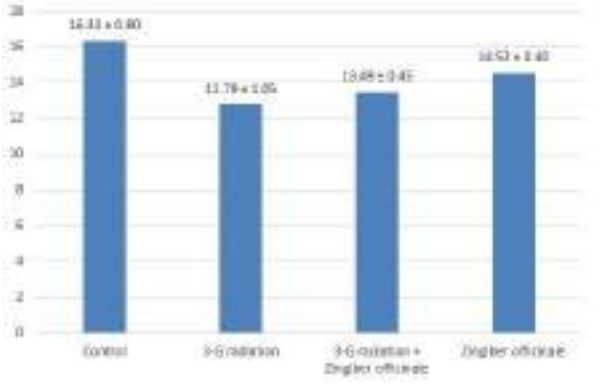
RESULTS

The mean values of thickness of granular layer in groups A, B, C and D are shown in figure-1. The results showed a highly significant decrease in the thickness of granular layer in 3G radiation treated group B as compared to control (p-value, 0.004). The data also revealed a highly significant restoration of granular layer thickness in radiation with ginger-treated group C (p-value, 0.009) when compared with group B. An insignificant decrease was also observed when ginger-treated group D was compared with control group A (figure-1).



Where n is the number of albino rats
Data is presented as Mean ± SEM (Standard Error of Mean)

Figure No.1: Thickness of Granular layer (µm) in different groups of Albino rats



Where n is the number of albino rats
Data is presented as Mean ± SEM (Standard Error of Mean)

Figure No.2: Mean Diameter of Purkinje Cell (µm) in different Groups of Albino Rats

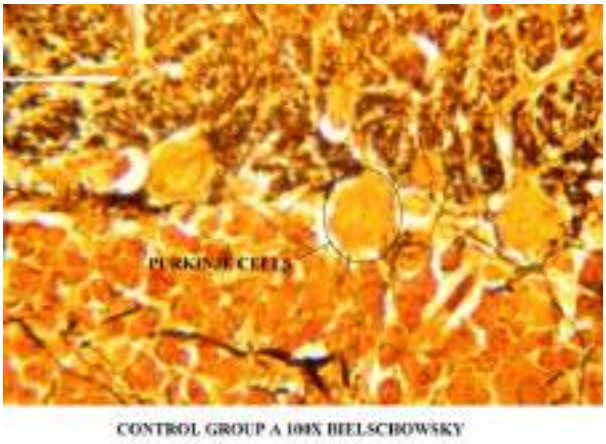


Figure No.3: Bielschowsky stained tissue section from cerebellum of control group A

Bielschowsky stained, 4µm thick section of control rat brain (cerebellum) showing Purkinje cells layer and pyramid-shaped Purkinje cells (Photomicrograph X 1000)

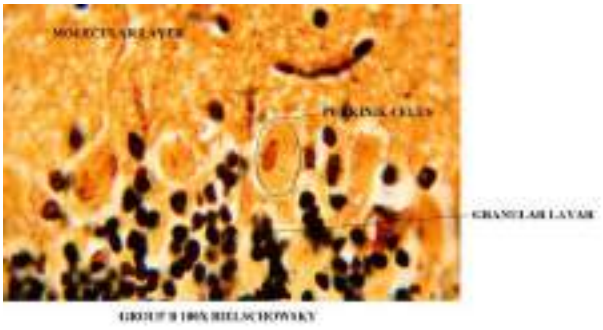


Figure No.4: Bielschowsky stained tissue section from cerebellum of mobile phone radiation treated group B

Bielschowsky stained, 4µm thick section of irradiated rat brain (cerebellum) showing decreased diameter of Purkinje cell with oedematous and degenerating nucleus. The Molecular & Granular Layers are also visible (Photomicrograph X 1000)

The mean values of diameter of Purkinje cell (µm) in group A, B, C and D are shown in figure-2. The size of Purkinje cell was significantly decreased in radiation-treated group B when compared to control group A (P value 0.012). However, insignificant restoration of Purkinje cell diameter was observed when radiation with ginger-treated group C was compared with radiation treated group B (p-value, 0.903). The mean value of Purkinje cell diameter in ginger-treated group D was near to control group A (figure-2).

On observation of Bielschowsky stained sections under oil immersion objective (100X), the Purkinje cells were seen as large pyramidal cells with apex directed towards the molecular layer and base towards the granular layer, lying in a regular pattern between molecular and granular layers (figure-3). The nerve fibers were seen as darkly stained fibers running in the molecular layer, parallel to Purkinje cell layer (figure-3).

Bielschowsky stained sections of cerebellar tissue from radiation treated group B animals under oil immersion lens showed dysmorphic changes in Purkinje cells represented by pyknosis of nuclei and reduction in their size, with shrinkage and degeneration of cell organelles. Granular layer also showed degeneration and nuclear accumulation with edematous spaces (figure-4).

Bielschowsky stained sections of group C animals (radiation with ginger) revealed restoration of cerebellar architecture similar to control (figure-3).

DISCUSSION

The most effective tool for communication these days are mobile phones. However, their use is associated with emission of radiofrequency radiation which has raised concerns about the safety related with their use[13]. Various effects of radiofrequency radiations have been reported in former studies, such as increased cellular excitability, lipid peroxidation, or enhanced stimulation of cellular reaction to stress etc[14]. Contrarily, literature search also reported absence of measurable biological effects of radiation on brain[15]. In view of these controversies, this study was conceived to detect microscopic anatomical changes in rat cerebellum in response to radiofrequency radiation emitted by third generation mobile phones.

The thickness of granular layer was highly significantly reduced in radiation exposed group B rats as compared to control. Marked improvement in thickness of granular layer was observed in histological sections taken from group C rats who were administered ginger in addition to radiation exposure. Hamzeh et al (2017)[16] observed significant improvement in level of anti-oxidants in rat brain in rats which were treated with ginger in addition to Diazinon as compared to Diazinon- treated group. This findings further show that histopathological effects leading to decreased thickness of granular layer are mediated by oxidative injury, which showed improvement in group C as rats assigned to this group consumed ginger along with RF radiation exposure, minimizing the effects of brain damage.

Degeneration of Purkinje cells was observed with decrease in the diameter of Purkinje cells in radiation treated group B tissue sections. Our results were similar to another study[17] who also observed reduced diameter of Purkinje cells in cerebellum of patients suffering from Alzheimer's disease as compared to senile controls. There was an insignificant restoration of the diameter of Purkinje cell diameter in group C receiving ginger in addition to 3G mobile phone emitted RF radiation. Ginger protects the brain by enhancing it's anti-oxidant defence system and down-regulation of MDA- levels to normal range as seen by a former study[18].

The Bielschowsky stained section from radiation treated group B showed disruption of architecture of cerebellar cortex, with dysmorphic Purkinje cells showing nuclear pyknosis and degeneration of other organelles. The molecular layer revealed decreased number of nerve fibers and granular layer showed disruption with degenerating neuron cell bodies. These findings were most likely due to the inflammatory process in the brain as a result of oxidative stress. Even though the duration of study was only 8 weeks, but these changes suggest that radiation emitted by third generation mobile phone produces histopathological changes which will be more enhanced longer the duration of exposure, and more advanced in the technology such as 4G mobile phones which are more common these days[19]. Numerous studies have determined excess production of reactive oxygen species (ROS) in experimental animals on exposure to radiofrequency radiation generated by mobile phones leading to oxidative damage to tissues, especially to brain because of close proximity of cell phone to it while in use.[20,21] Shahabi et al (2018)[22] found more vacuoles and of larger sized in brain tissue of male wistar rats after exposing them to 900 MHz RF radiation for 6 hour/day for a duration of one and two months as compared to the controls. Similar findings were ascertained by Zymantiene et al (2020)[23] who observed decrease in the number of Purkinje cells, presence of vacuoles in neurons as well as glial cells and interstitial oedema in cerebellum of BALB/c mice exposed to 1375 MHz radiofrequency radiation emitted by mobile phones continuously for 72 hours. Marked improvement in cerebellar architecture was observed in tissue slides of cerebellar cortex from radiation with ginger treated group C. These were most likely due to the anti-oxidant effects of ginger as it protects tissues from oxidative stress decreasing their inflammation. These results have been reported in previous studies as well[16,24]. These findings were in conformity to Sangi et al (2020)[19] who also observed significant improvement in microscopic architecture of cerebellar cortex in male Wistar albino rats exposed to mobile phones for 4 weeks with concomitant use of vitamin E in a dose of 50IU/Kg body weight. This shows that vitamin E, which is also a potent anti-oxidant like ginger, protected brain tissue from oxidative stress induced by cell phones, by removal of free radicals, stabilization of cell membranes and decreasing inflammatory changes in brain tissue.

Continuous exposure to radiofrequency radiation generated by 3G mobile phones for 8 weeks cause damage to the brain leading to histopathological changes in cerebellum, which improved markedly by simultaneous use of ginger in their diet. The results of the study should be disseminated to health care workers so they can advice masses about the daily use of ginger in their diet.

CONCLUSION

The cerebellum of rat brain is sensitive to damage by radiofrequency radiations emitted by cell phones. However, ginger minimizes these damaging effects when used simultaneously.

Author's Contribution:

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Original Article

Clinical Profile and Out Come of Diabetic Keto Acidosis in Emergency Department

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ABSTRACT

Objective: To ascertain the frequencies of presentations, biochemical profile compliance, comorbidities and outcomes of DKA, HHS and hypoglycemia.

Study Design: cross-sectional study

Place and Duration of Study: This study was conducted at emergency department of Ayub Teaching Hospital Abbottabad from June 2018 to December 2018.

Materials and Methods: All DKA, HHS and hypoglycemic patients presented in emergency department are included in study. We recorded demographic variables, clinical characteristics, chief complaints, comorbidities, hospital stay and outcome of complications. Anthropometric measures include pulse, blood pressure, respiratory rate, SPO2, GCS and temperature

Results: 197 diabetic patients were included in study. The mean age of sample was 53±18.84. 90/197 (45%) diabetic diagnosed individuals fulfilled HHS criteria. 57/197 patients (28%) met criteria of DKA, and 50/197 patients (25%) had hypoglycemia on presentation. The most common presentation of HHS and hypoglycemia was altered conscious level while majority of DKA were received in shock at presentation. The mean RBS of HHS, DKA, and hypoglycemic patients was 986mg/dl, 453mg/dl and 70mg/dl respectively. Glycosylated hemoglobin of HHS, DKA and hypoglycemia was 9.9, 9.4 and 6.5millimole respectively. 26 HHS patients died during management, 59 had comorbidities and common comorbidity was cardiovascular diseases (27%). 7 DKA patients died during management, 15 had underlying comorbidities. Renal comorbidities were commonly recorded. 2 hypoglycemic patients died during management, 28 had comorbidity and renal comorbidity was common. 81 HHS patients had poor compliance, 36 DKA had poor compliance and 19 hypoglycemics were poorly compliant to medications.

Conclusion: Highest mortality was recorded in HHS patients which is likely due to old age, cardiovascular comorbidities and poor compliance.

Key Words: Hypoglycemia, hyperosmolar hyperglycemic state (HHS), emergency department (ED), diabetic ketoacidosis (DKA), comorbidity, compliance

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INTRODUCTION

Diabetes is a chronic lifelong disease with which patient have to live. Diabetic patients frequently present with micro-vascular and macro-vascular complications. Among 26.3% of known diabetic Pakistani population, 19.2% are diagnosed and 7.1% are newly diagnosed.[1]

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Fatalities of acute complications, in elder diabetic population (age>50) are 40% while, 3% in younger individuals[2]. DKA with 3% annual increase in global incidence rate since 1980s is most common disease in children[3]. Patients with diabetic ketoacidosis classically present with triad of metabolic acidosis, hyperglycemia and hyperketonemia. With increase in prevalence of type 2 diabetes, DKA is not uncommon in type 2 diabetes mellitus (NIDDM) patients[4 10 9].

Hyperglycemic hyperosmolar state is altered mental status caused by hyperosmolarity, profound dehydration and severe hyperglycemia without significant ketosis[5]. Intensively treated (3-fold) diabetic patients who are on triple therapy and insulin respectively, have increased risk of hypoglycemia the most feared complication[6]. Severe hypoglycemia prolongs hospital stay of diabetic patient with increase prevalence of dementia[7]. Diabetic patients requiring emergency care for hypoglycemia have risks for long term mortality[8].

In Pakistan, people having little access to primary health care facility are presented to emergency department for diabetes related illness. Moreover, poor compliance to medication made frequent presentation to emergency department with complications[9]. Higher rate of non-compliance to medication among diabetic patients is noted in studies[4,6.] About 5 million deaths occur annually due to diabetes related complications in developing countries. As Pakistan is developing country its 28.3% urban and 25.3% rural population are diabetic[1]. So, emergencies regarding diabetes remain an important clinical problem among inhabitants of Pakistan. Surprisingly very little studies are conducted regarding clinical presentations, complication´s frequency, patient´s compliance, underlying diseases, outcomes and mortality in diabetic population.

MATERIALS AND METHODS

This cross-sectional study was undertaken at Ayub Teaching Hospital, a tertiary care hospital in Abbottabad, from 1st June 2018 to 31st December 2018. In these review demographic variable, clinical presentations, anthropometric measures and blood chemistry were recorded.

Anthropometric Measures: Patient was quickly evaluated by accessing blood pressure, respiratory rate, axillary temperature, Glasgow coma scale and oxygen saturation.

Chemistry: Include random blood sugar, fasting blood sugar, arterial blood gases, serum electrolytes, blood urea, blood creatinine and urine routine examination with ketones.

Patients diagnosed and labeled by clinicians as DKA, HHS and hypoglycemia were included in study. Data has been analyzed in IBM SPSS Statistics V.21. The level of statistical significance was set at 5%.

RESULTS

In 7-month study 200 people were selected but 3 refused to give consent (n=197). [90(45%) were male, 107(54%) were female] from the emergency department (ED) of Ayub Teaching Hospital.

Mean age of sample was 53±18.84 (age range 14-98 years). The most common emergencies encountered overall in diabetic population were: Ninety patients presented with HHS (45%), fifty-seven presented with DKA (28%), fifty presented with hypoglycemic emergencies (25%).

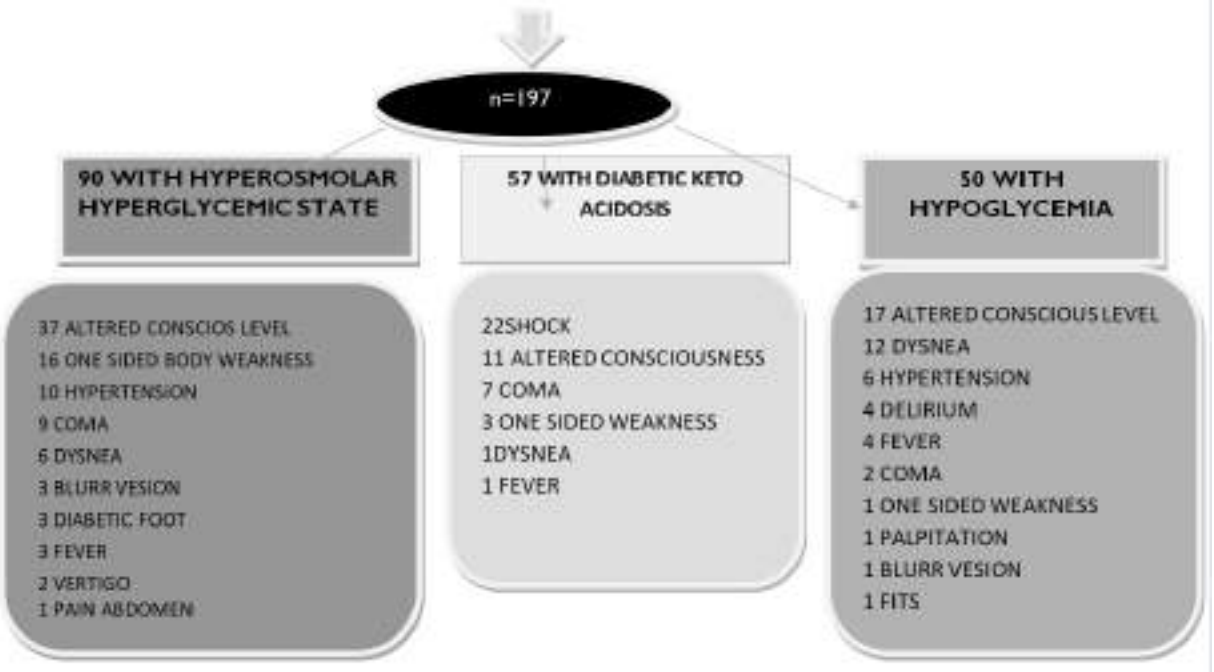

Figure No.1: Frequency of Diabetic Glycemic Emergencies encountedred in Emergency Department

Table No.1: Group statistics of diabetic patients presented in emergency

Variables		HHS (n=90)	Sig	**DKA** (n=57)	Sig	**Hypoglycemia** (n=50)	Sig
Diabetes	Type1	0	0.000	36	0.000	3	0.003
	Type2	90		21		47	
Urinary Ketone	+4	0	0.000	6	0.000	4	0.000
	+3	5		46		0	
	+2	5		5		3	
	0	80		0		43	

Urinary Glucose	+4		2		0.000	10		0.000	0		0.000
	+3		78			46			6		
	+2		8			1			5		
	0		2			0			39		
Arterial Blood Gases	Metabolic acidosis		28		0.005	53		0.000	6		0.005
	Normal		62			3			41		
	Missed		0			1			3		
Serum Sodium	>145		1		0.521	1		0.19	0		0.009
	<135		22			18			4		
	135-145		66			38			46		
Serum Potassium	>5		19		0.273	25		0.000	5		0.012
	<3.5		2			4			1		
	3.5-5		68			28			44		
Medication Used	Insulin		2		0.000	22		0.000	4		0.002
	Oral		82			16			45		
	Both		4			6			1		
	Not used		2			13			0		
Compliance	Poor		81			36		0.000	19		
	Good		7			4			31		
	Newly diagnosed		2			17			0		
Comorbidities	No		31		0.001	52		0.513	22		0.000
	Yes	Renal	59	14		15	7		28	20	
		Cardiac		25			4			7	
		CVA		16			3			0	
		Chronic pulmonary diseases		1			1			0	
		Liver Disease		3			0			1	
Outcome	Improved		64			50		0.15	48		
	Died		26			7			2		

DISCUSSION

To our knowledge this is first national study which is reporting frequency of diabetic presentations in emergency department. Also there is no recent data available on frequency of diabetic presentations internationally.

In present study, mean age was 53±18. This is older than National Diabetic Survey of Pakistan (NDSP) according to which mean age is 43±14[1]. This is probably due to large sample size of NDSP. The first most emergency encountered was HHS 90/200(45%), DKA 57/200(28.5%) and with hypoglycemia 50(25%). Remaining 3 patients did not fulfilled criteria of HHS, DKA and hypoglycemia.

The two common presentations of HHS were altered conscious level[7] 37/90(41%) followed by body weakness 16/90(17%). An old American study states weakness as a most common presentation (21/22) and altered conscious state the second common presentation (13/22) Khardori R et al [13]. This might be due to small sample size of American study. The mean age of HHS patients was 61±13 in contrast to American study which had age of 68.5±3.9. Other studies Macisacc et al [14] reports 69±1.7 which is also older than our HHS patients. Random blood sugar of present study HHS patients was 986mg/dl±84 which is almost consistent with macisacc et al and Kitabchi et al [15]. 90% HHS patients have normal ketone in urine. Kitabchi et al reports that HHS patients have low ketone level (β hydroxy butarate) 1.02 as compared to high 9.4 in DKA. 26/90 HHS patients died with mortality of 28%, this is very high as compared to macisacc et al which reports 17%. This can be explained by higher rate of underlying comorbidity. 59/90 had comorbidity, the common comorbidity was cardiovascular disease. Also the high mean blood pressure (143/93) was noted in HSS patients and the glycemic control of HHS patients was poor. The mean Hb1ac level was 9.9±2. Compliance in HHS patients was poor. Only 10% had good compliance. Higher rate of cardiac comorbidity, poor glycemic control and poor compliance can be the causes of high mortality in HSS patients.

Second most common emergency encountered was DKA. Majority of patients presented in shock 22/57(38%), followed by altered conscious level 11/57(19%) and 7/57(12%) in coma. Dehydration and altered mental status in DKA were also highlighted on

physical examination by study published in US [7]. A study done at Taiwan report nausea/vomiting the most common manifestation followed by drowsiness, dyspnea, polyurea and abdominal pain sue-Fu Lin et at[17]. The mean age at onset of DKA was 35±17 years in our study while most of DKA patients in Sue-Fu Lin, et al[17] was >40 years. In present study mean age of DKA is almost consistent with mean age in Macisacc et al[14] that is 33 years. Another Pakistani study reports mean age of DKA was 48±7 years A Jabbar et al[16]. 36/57(63%) DKA patients were type 1 diabetics and 22/57(38%) were type 2 diabetics[15]. 53/57(92%) DKA had metabolic acidosis consistent with Macisacc et al[14] (PH=7.1) and A Jabbar et al (PH=7.07). Random blood sugar of our study was 453mg/dl a little lower than Macisacc et al (RBS=504mg/dl) and A. Jabbar et al[16] (RBS=628mg/dl). Potassium level of DKA patients in present study was 43% hyperkalemic and 49% normokalaemia while A. Jabbar et al have mean value of potassium 4.9. In our study 100% DKA patients were urinary ketone positive, consistent with Kitabchi et al[15] which have ketone level of 9.1 (β hydroxybutyrate). During management of DKA patients, 7 patients died having mortality of 12% which is quite lower than reported by A. Jabbar et al. 36/57(63%) DKA patients had poor compliance, which was also found to be precipitating factor for DKA in 59% cases[10]. 15/57(26%) patients had underlying comorbidity. Renal comorbidity was prevalent in DKA patients.

17(29%) DKA patients were newly diagnosed type 1 diabetics, Sohail Bashir Sulehria et al [10] reports 23% newly diagnosed DKA while 2 HHS patients were newly diagnosed type 2 diabetics. As type 1 have more genetic pattern, increased incidence of type 1 can be due to intermarriages between cousins in Pakistani culture.

Hypoglycemia was third emergency 50/200 that was encountered in emergency department. Mostly hypoglycemic patients manifest in emergency with altered conscious level 17/50 followed by dyspnea 12/50, hypertension 6/50. This is not matched with Rajendran. R et al[8] which report unconscious (collapse) common hypoglycemic manifestation followed by confusion. Mean age of hypoglycemic patients was 58±15 which is younger than Rajendran R et al, this can be due to small size of our sample. 45/50(90%) hypoglycemic patients use oral hypoglycemic agent, Rajendran R et al states one third hypoglycemia is due to oral sulfonylureas, while Deusenberry CM et al [18] establish that hypoglycemia is common with oral hypoglycemics. 31/50 hypoglycemic patients had good compliance. 56% have comorbidity, it is depicted that renal comorbidity is prevalent in hypoglycemic patients [8,18], during management 48 improved and 2 died with mortality of 4%.

To the best of author's knowledge, literature is deficient regarding frequencies of diabetic patients with acute glycemic emergencies in Pakistan. So, results were mostly compared with studies of other countries. This study is important in two ways first for treating physician regarding different frequency figures of diabetic emergencies as a whole and then in various disease groups, secondly this study should serve as basis for future research in management and prevention of diabetic emergencies. At this point it is important to highlight that this is data from one journal tertiary care hospital. There is lot more to see in other hospitals which may also have adequate managements for complications, outcomes, mortalities etc.

CONCLUSION

Diabetes emergencies were predominant in female gender. HHS was most common emergency followed by DKA and hypoglycemia. HHS and hypoglycemia were prevalent in type 2 diabetes mellitus while DKA was prevalent in type 1 diabetes mellitus. Common presentation of HHS and hypoglycemia was altered conscious level while majority DKA manifest as shock. HHS patients were older than hypoglycemic and DKA patients. Type 2 diabetes was more prevalent in population while type 1 was prevalent in newly diagnosed diabetic patients. Overall compliance of the patients was very poor. Renal comorbidities were common in DKA and hypoglycemic patients while cardiovascular comorbidities were common in HHS patients. Highest mortality was recorded in HHS patients which t is likely due to old age, cardiovascular comorbidities and poor compliance.

Author's Contribution:

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