

# Serum Bilirubin and G-Glutamyl Transferase in Female Patients Suffering from Migraine

Bilirubin and Liver Aminotransferase in Migraine of Females

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## ABSTRACT

**Objective:** To analyze serum bilirubin and liver aminotransferase in migraine female patients at a tertiary care hospital of Sindh.

**Study Design:** Cross sectional study

**Place and Duration of Study:** This study was conducted at the Department of Medicine, Isra University Hospitals from February 2019 to January 2020.

**Materials and Methods:** A sample of 100 diagnosed cases of migraine and 100 controls was selected according criteria. Severity of migraine headache was defined according to the Visual Analogue Scale (VAS). 5 ml blood was drawn; 2 ml was put in EDTA bottles for blood parameters and 3 ml was centrifuged to get sera for detection of liver function tests. Data was analyzed on statistical software SPSS (ver 21.0) by Student t-test (at  $P \leq 0.05$ ) and correlation by Spearman's rho testing.

**Results:** Total, Direct and Indirect bilirubin in control and migraine patients were noted as  $1.24 \pm 0.09$  and  $1.07 \pm 0.08$  mg/dl ( $P=0.0001$ ),  $0.86 \pm 0.09$  and  $0.71 \pm 0.04$  mg/dl ( $P=0.0001$ ),  $0.27 \pm 0.08$  and  $0.23 \pm 0.09$  mg/dl ( $P=0.001$ ) respectively. GGT in control was  $36.3 \pm 6.09$  IU compared to migraine patients as  $44.9 \pm 8.3$  IU. Total bilirubin, direct and indirect bilirubin reveals negative correlation with migraine severity, while gamma glutamyl transferase (GGT) reveals positive correlation.

**Conclusion:** The present prospective study found low serum bilirubin and raised gamma – glutamyl transferase levels in migraine patients.

**Key Words:** Bilirubin, Migraine, G-glutamyl transferase

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## INTRODUCTION

Migraine is a common health problem particularly in the women. Migraine is a vascular type headache and most common neurological diseases in all age groups. Migraine causes frustration and sufferance in migraineurs. It affects 12 – 15% adults in Western countries.<sup>1</sup> Migraine is characterized by throbbing headache, tearing eyes, vertigo, nausea, photobia, phonophobia, and tinnitus and in hemiplegia in severe cases. Studies<sup>1,2</sup> show the migraine patients are at increased risk of coronary artery disease. Clinical research has confirmed the increased cerebrovascular accident symptomatology in migraineurs and a remarkable role in migrainous infarction and

hemiplegia. Migraineur should be given special clinical attention for preventing complications.<sup>3</sup>

Recently, many biochemical markers have been suggested play role in migraine and clinical risk factors have been studied.<sup>4,5</sup> Bilirubin is one of clinical risk factor that has got attention in clinical research. Bilirubin is a toxic metabolite of heme catabolism. Bilirubin has demonstrated anti – oxidant and cytoprotective potential in recent studies.<sup>6-8</sup> It has been reported the bilirubin influences the Fc receptor expression in phagocytic cells that indicates its immunomodulatory role in migrains.<sup>9</sup> Bilirubin is reported reduce the produce of Interleukin – 2 (IL – 2) in lymphocytes.<sup>10</sup> Obviously, the bilirubin is a vital anti – oxidant and anti – inflammatory substance. Serum bilirubin has been used to stratify the arterial – stiffness in coronary artery disease patients.<sup>11</sup> Serum has been associated with GFR (glomerular filtration rate) and is correlated with decreasing renal functioning general populations.<sup>12</sup> Research<sup>13,14</sup> has proved correlation of serum bilirubin with systemic hypertension and multiple sclerosis patients positively. However, the association of serum bilirubin and migraine are not discussed well in medical literature. The present study was conducted to analyze the serum bilirubin in female patients suffering from migraine and its correlation with visual analogue scale presenting at our tertiary care

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hospital. The objective of study was to analyze serum bilirubin levels in migraine patients in comparison to controls and correlation with bilirubin subtypes in migraineurs.

**MATERIALS AND METHODS**

The present cross sectional study was conducted at Department of Medicine, Isra University Hospitals from February 2019 to January 2020. Study was approved by ethical review committee for research purpose. Sample was calculated by “sampling-proportions” using online Rao software. A sample of 100 diagnosed cases of migraine and 100 controls was selected. Inclusion criteria were; female diagnosed migraine and age 20- 40 years. Migraine was defined as per international criteria.<sup>16</sup> Severity of migraine headache was defined according to the Visual Analogue Scale (VAS).<sup>17</sup> VAS 0 – 10 numeric pain rating scale was used. 0 – no pain, 1 -5 moderate pain and 6 – 10 was severe pain. Controls were taken from the attendants of patients. Control were age and demography matched. Female patients suffering from concomitant morbidities were excluded. Systemic hypertension, anxiety tensions, depression, diabetes mellitus, chronic inflammatory lung and kidney diseases, viral hepatitis, and metabolic syndrome were excluded from study protocol. Volunteers were asked inclusion in study protocol voluntarily and abide by the protocol. Cases and control clinical history was taken to reach to the inclusion criteria. Data was entered in a proforma and kept confidential. Vitals were checked and noted. Participants were asked for blood sampling. 5 ml blood was drawn in Disposable syringe (BD, USA) from ante cubital vein. 2 ml was put in EDTA bottles for blood parameters. 3 ml was centrifuged to get sera for detection of liver parameters. Bilirubin – total, direct and indirect and liver aminotransferases – alanine transaminase (ALT), alkaline phosphatase (ALP) and Gamma glutamyl transferase (GGT) were analyzed on Cobas Roche Analyzer. Analyzer is fully automated equipment. Data was analyzed on statistical software SPSS (ver 21.0). Numerical variables, e.g. age, vitals, blood and liver functions tests were analyzed by Student t-test. Correlation of bilirubin and aminotransferases was calculated by Spearman`s rho testing. Scatter plots were plotted on Microsoft Excel sheet. Statistical level of significance was taken at  $P \leq 0.05$ .

**RESULTS**

Demography, physical and laboratory findings are summarized in table 1. All comparisons in table – 1 are non- significant that shows the study subject groups were matched. Table – 2 shows the liver function tests that shows significant differences between control and migraine patients for the total bilirubin, direct and

indirect bilirubin and the gamma glutamyl transferase (GGT) ( $P \leq 0.001$ ).

**Table No.1: Demography and Laboratory findings (n=200)**

	Control	Migraine	P
Age (years)	33.5±3.5	32.7±7.5	0.71
Body weight (kg)	77.4±12.2	78.45±13.9	0.56
Systolic BP (mmHg)	131.3±5.2	130.58±8.54	0.46
Diastolic BP (mmHg)	80.4±14.8	70.8±8.5	0.34
PCV (Hct.) (%)	41.3±3.3	41.5±3.7	0.79
Hemoglobin (grams)	11.3 ±1.3	11.5±1.5	0.91
Red Blood Cells (x10 <sup>6</sup> )	3.7 ±0.2	3.6±0.5	0.91
White Blood Cells (x10 <sup>3</sup> )	4.7 ±0.3	5.0±0.3	0.71
Platelet counts (x10 <sup>9</sup> )	151.3±5.1	149.5±9.1	0.67

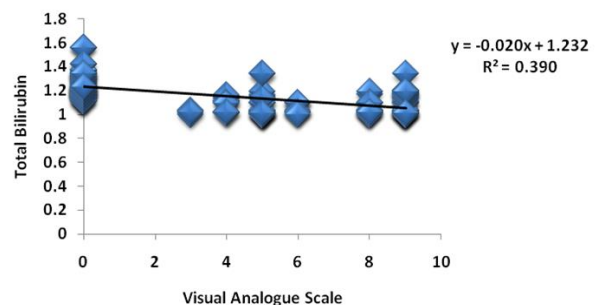
**Table No.2: Liver function test (n=200)**

	Control	Migraine	P
Total bilirubin	1.24±0.09	1.07±0.08	0.0001
Direct bilirubin	0.86±0.09	0.71±0.04	0.0001
Indirect bilirubin	0.27±0.08	0.23±0.09	0.001
ALT	33.7±5.6	33.9±5.7	0.39
ALP	80.6±14.9	82.4±14.3	0.94
GGT	36.3±6.09	44.9±8.3	0.0001

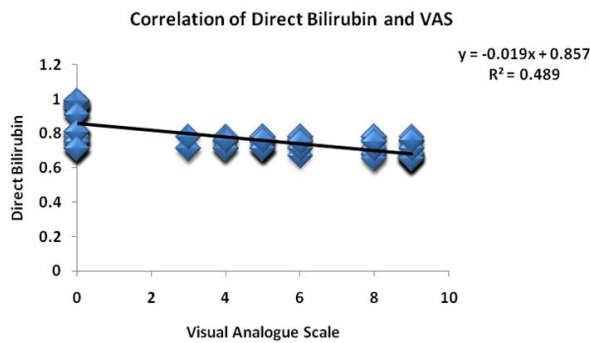
**Table 3. Migraine Pain Severity – Correlation of Liver function tests and Visual Analogue Scale**

	Total Bilirubin	Direct Bilirubin	Indirect Bilirubin	ALT	ALP	GGT
r-value	-0.663	-0.751	-0.433	0.012	0.075	0.631
P-value	0.0001	0.0001	0.0001	0.865	0.290	0.0001
N	200	200	200	200	200	200

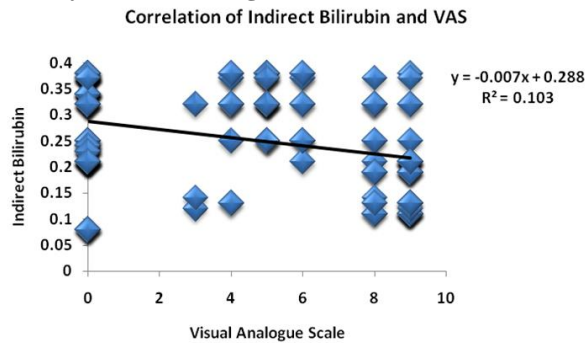
**Correlation of Total Bilirubin and VAS**



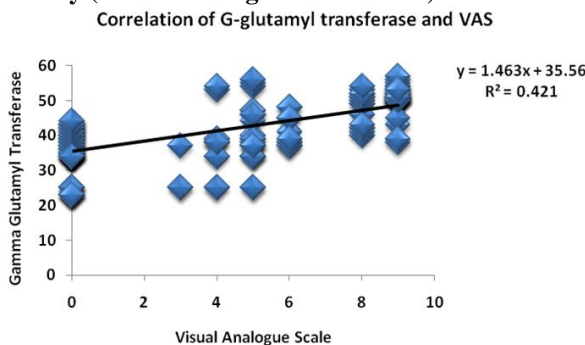
**Figure No.1: Scatter plot showing negative correlation of total bilirubin and migraine pain severity (Visual Analogue Scale - VSA)**



**Figure No.2: Scatter plot showing negative correlation of direct bilirubin and migraine pain severity (Visual Analogue Scale - VSA)**



**Figure No.3: Scatter plot showing negative correlation of indirect bilirubin and migraine pain severity (Visual Analogue Scale - VSA)**



**Figure No.4: Scatter plot showing positive correlation of gamma glutamyl transferase and migraine pain severity (Visual Analogue Scale - VSA)**

Total, Direct and Indirect bilirubin in control and migraine patients were noted  $1.24 \pm 0.09$  and  $1.07 \pm 0.08$  mg/dl ( $P=0.0001$ ),  $0.86 \pm 0.09$  and  $0.71 \pm 0.04$  mg/dl ( $P=0.0001$ ),  $0.27 \pm 0.08$  and  $0.23 \pm 0.09$  mg/dl ( $P=0.001$ ) respectively. GGT in control was  $36.3 \pm 6.09$  IU compared to migraine patients as  $44.9 \pm 8.3$  IU. Total bilirubin, direct and indirect bilirubin reveals negative correlation with migraine severity (Visual analogue scale) (Scatter plots 1 – 3), while gamma glutamyl transferase (GGT) reveals positive correlation with VAS as shown in table 3 (Scatter plot 4).

**DISCUSSION**

The present cross sectional case – control study analyzed the total, direct and indirect bilirubins and liver aminotransferases in female diagnosed migraine cases compared to control.

We found low levels of total, direct and indirect bilirubin in migraine cases compared to controls ( $P<0.001$ ) and gamma glutamyl transferase (GGT) was high. The findings are consistent with previous studies.<sup>17-21</sup> However, raised GGT is a new finding being reported for the first time. In present study the total, direct and indirect bilirubin in control and migraine patients were noted  $1.24 \pm 0.09$  and  $1.07 \pm 0.08$  mg/dl ( $P=0.0001$ ),  $0.86 \pm 0.09$  and  $0.71 \pm 0.04$  mg/dl ( $P=0.0001$ ),  $0.27 \pm 0.08$  and  $0.23 \pm 0.09$  mg/dl ( $P=0.001$ ) respectively. GGT in control was  $36.3 \pm 6.09$  IU compared to migraine patients as  $44.9 \pm 8.3$  IU. Serum bilirubin has been associated with different diseases such as cigarette smokers, systemic hypertension, cardiovascular diseases, etc.<sup>17-21</sup> A previous study<sup>18</sup> concluded, the serum bilirubin significantly protects against the atherosclerosis. Various studies<sup>19-21</sup> had attested the serum bilirubin is negative correlated with coronary artery disease in patients suffering from obesity, diabetes mellitus, metabolic syndrome, and cigarette smokers. A recent study<sup>21</sup> reported evidence of low serum bilirubin in migraine patients and it may be used a biomarker of neurogenic inflammation in this particular patient group. This is a consistent finding to the present study. A previous study<sup>12</sup> conducted large study with sample of 2784 individuals reported low serum bilirubin in chronic kidney patients and may be used as a potential risk factor of declining renal function. This is in support to the present study that the serum bilirubin is a potential biomarker in migraine patients. The low serum bilirubin in particular disease has been attributed to its anti – oxidant properties. Bilirubin inhibits oxidative stress, is used up there hence levels are low. Bilirubin helps as anti – oxidant in neutralizing the reactive oxygen species (ROS).<sup>21-23</sup> Previous studies<sup>24,25</sup> had reported association of bilirubin in migraine, brain stroke, coronary artery disease and atherosclerosis, etc. Neurogenic inflammation of migraine increases the oxidative stress and this is removed by bilirubin hence used up and its concentrations fall that has been noted in the present study too.<sup>26,27</sup> Many studies have witnessed significant inflammation in migraine patients where large pro – inflammatory cytokines are secreted; stimulate nerve endings resulting in severe pain.<sup>28</sup> Anti – inflammatory drugs have been considered effective in alleviating migraine pain.<sup>29</sup> Neurogenic inflammation and oxidative stress in migraine patients lowers the serum bilirubin concentrations.<sup>21</sup> GGT was found elevated in migraine patient that is a new finding and needs further elaboration of underlying mechanism. Present study is worth report on low serum bilirubin in migraine patients. Only limitation of present study is the small

sample size of peculiar ethnicity, hence findings may not be generalized to other populations of different geographical areas.

## CONCLUSION

The present prospective study found low serum bilirubin concentration in migraine patients. However, gamma – glutamyl transferase activity was found elevated. Low serum bilirubin indicates increased oxidative stress in migraine patients due to the neurogenic inflammation.

### Author's Contribution:

Concept & Design of Study: Akram Munir  
 Drafting: Muhammad Akbar  
 Data Analysis: Muhammad Akbar  
 Revisiting Critically: Akram Munir, Muhammad Akbar  
 Final Approval of version: Akram Munir

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

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