Original Article

Serum CTX-I Levels

Association of Serum CTX-I Levels with Hormone Replacement and Interleukin Inhibitor Therapy in Peri-Menopausal Women Presenting in a Tertiary Care Hospital of Peshawar, KPK

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ABSTRACT

Objective: To determine the association of serum CTX-I levels with hormone replacement and interleukin inhibitortherapies

Study Design: Descriptive cross sectional study

Place and Duration of Study: This study was conducted at the Hayatabad Medical Complex (HMC), Peshawar from June 2012 to August 2012.

Materials and Methods: A total of 100 peri-menopausal women were included in the study to determine the association of serum of CTX-I levels with hormone replacement therapy (HRT) and interleukin inhibitors. These females were randomly selected and screened for osteoporosis. The age of study population was between 45-55 years. Informed consent was taken. Detailed history was obtained regarding occupation, income, family history, number of pregnancies and medications. Women with complaints of joint pains, history of osteoarthritis, rheumatoid arthritis and any other bone disease were excluded from the study. They were radiologically assessed for osteoporosis by using Singh index as I to VI. Ethical approval for the study was taken from the Institutional Ethical Research Committee (IERC) of HMC. Blood samples were taken for estimation of hemoglobin, ESR, calcium, alkaline phosphatase and CTX-I.

Results: The levels of CTX-I were elevated in peri-menopausal women who were radiographically diagnosed as osteoporotic patients. However CTX-I levels were either normal or insignificantly raised in women taking either HRT or interleukin inhibitors. The data were subjected to statistical analysis using Chi-square test on computer software SPSS-17. Results were expressed in form of tables.

Association and their significance were sorted out on the software. There was a significant association of CTX-I levels with both HRT & interleukin inhibitors ($p = 0.000$)

Conclusion: This study revealed a significant association of serum CTX-I levels with both hormone replacement and interleukin inhibitor therapies.

Key Words: osteoporosis, CTX-I, hormone replacement therapy, peri-menopausal women

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INTRODUCTION

Osteoporosis is a global problem of old age caused by more bone resorption as compared to bone formation. Osteoporotic bones are prone to fractures leading to disability and treatment costs. Majority of postmenopausal women suffer from osteoporosis. This is caused by deficiency of estrogen leading to excessive bone loss. It is classified as one of public health problems and treated as a social disease.[1]

According to the estimated data of the National Osteoporosis Foundation (USA), every second woman at the age of 50 years experiences an osteoporosis fracture, and the risk of such fracture in women is higher than the risk of breast, ovary or uterus body cancers together.[2]

According to Peters et al., a high calcium intake may decrease the osteoporosis fracture risk as much as by 60% due to the fact that it plays an important role in decreasing the bone remodeling and age-related bone mass loss.[3]

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Bone is constantly repaired and remodeled. Approximately 20% bone tissue is replaced annually varying by site and type.[4] The prevalence of osteoporosis increases with age. Bone loss is reportedly more rapid in females in the first few years post menopause and is influenced by estrogen deficiency. [5] The World Health Organization (WHO) has defined osteoporosis as bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) 2.5 standard deviations (SD) or more below the mean peak bone mass of premenopausal females (T-score ≤ - 2.5 SD).[6] Technical developments in the measurement of BMD have led to its adoption as the standard for diagnosis of osteoporosis, however its relatively poor sensitivity contrasting with high specificity means that many potential fractures will be missed if BMD assessment is used alone.[7]

During the past decade, bone turnover markers (BTMs) have been established as tools in the clinical management of bone disease in addition to their use in research for a long time. The majority of bone resorption markers are degradation products of collagen. These markers have become the preferred means of measuring resorption and examples include carboxy-terminal and amino-terminal cross-linked telopeptide of type I collagen (CTX and NTX respectively).

CTX is a marker of bone degradation. It is derived from the enzymatic degradation (hydrolysis) of type I collagen; CTX is a peptide related to regions of cross linking with pyridinoline.[8, 9]

Type I collagen comprises over 90% of the total bone protein. High levels of CTX-I are indicative of excessive bone degradation and indicate osteoporosis. It is a sensitive marker for bone resorption in osteolytic diseases such as osteoporosis and osteoarthritis.[8] Bones continuously remodel according to body requirement and resources. Osteoclasts are responsible for enzymatic hydrolysis of type I collagen. Acidic and neutral proteases break down collagen into fragments, releasing cross-linked N-terminal and C-terminal telopeptide CTX-I.[9] CTX-I, as biochemical marker of bone degradation, is the most sensitive marker to assess bone degradation and formation. [10] The normal serum levels of CTX-I range from 50-409 pg/ml.The major disadvantage of CTX is its large circadian variation necessitating a morning fasting sample for accurate interpretation. [11]

A comprehensive drug history should also be taken into account when interpreting bone marker levels. Anti-resorptive drugs such as bisphosphonates [12] and hormone replacement therapy (HRT) [13] have a major effect on markers of bone resorption and long-term corticosteroid therapy is known to suppress bone formation [14]

A large number of peri-menopausal women presenting in orthopedic outpatient department of HMC suffer from either backache or bone pains. They were assessed radiologically for any signs of osteoporosis. We conducted this study in order to determine the association of HRT and anti-resorptive therapy with the serum levels of CTX-I in these patients with radiological evidence of osteoporosis.

MATERIAL SAND METHODS

This descriptive cross-sectional study was carried out in a tertiary health care facility, Hayatabad Medical Complex (HMC), Peshawar, Pakistan to determine association of serum CTX-I levels with HRT and interleukin inhibitors in radiographically assessed peri-menopausal women. These females were randomly selected and screened for osteoporosis. After explaining aims and objectives, informed consent was taken from each subject for participation in study. Ethical approval for the study was taken from the Institutional Ethical Research Committee (IERC) of Postgraduate Medical Institute (PGMI), Peshawar. Sample size was 100 subjects and this was calculated by using 30% proportion of osteoporosis, 95% confidence level and 5% margin of error according to WHO software for sample size determination.

The age of women ranged from 45-55 years reporting to orthopedic outpatient department, HMC, Peshawar. Variables like age, age at marriage, education, husband's education, occupation and monthly income along with number of pregnancies, number of still births and number of alive children were recorded. ESR, serum albumin, serum calcium and serum alkaline phosphatase were determined as individual values to set control and to exclude any preexisting condition. The subjects having an ESR above 25 mm in 1st hour, alkaline phosphatase above 260 IU/L, serum albumin above 3 g/dL and subjects with comorbid diseases and any history of joint diseases were excluded from the study.

The analytic work was done in Pakistan Medical Research Council Research Centre, Khyber Medical College, Pathology laboratory of Institute of Kidney Diseases and PGMI, HMC, Peshawar. Subjects were also assessed according to their lifestyle, education, husband's education, occupation, monthly income, previous family history regarding the disease, previous medications like steroids, number of pregnancies, age in years, ambulatory status as community ambulant, house hold ambulant and bed ridden were recorded.

History of medication like HRT, interleukin inhibitors, anti-inflammatory drugs and any supplement was particularly obtained to determine the association of medication with CTX levels.

Hemoglobin in g/dL, ESR byWestergren method as millimeter in 1st hour, serum albumin (g/dL), serum calcium as mg/dL, serum alkaline phosphatase as international units per liter, radiographic grade of osteoporosis according to Singh index as I-VI and

CTX-I level in pg/ml were estimated. Association and their significance were sorted out on SPSS version 17. All individual variables were analyzed as independent variables. Chi-square test was applied to determine association of CTX levels with various variables and with osteoporosis.

RESULTS

The mean age of the study population was 48.24 years ± 2.78. The mean hemoglobin level was 10.85 g/dL ± 1.4. Serum CTX-I minimum level was 102 pg/ml and maximum level was 2016 pg/ml.

The mean values of CTX-I for Singh grades VI, V and IV were 454.69, 1047.64 and 1672.00 respectively. The average value was 574.45±41.65. On application of ANOVA on serum levels of CTX-I and Sigh grades, a P value of 0.05 was obtained showing a significant correlation with Singh index i.e. serum levels of CTX-I and radiographic index were negatively correlated with each other.

Seventy two percent subjects were taking supplements, 12% were taking interleukin inhibitors, 11% were taking anti-inflammatory drugs and 5% were on HRT. No subject on HRT was having more than double the normal value of CTX-I. Only two subject taking interleukin inhibitors had triple the normal value of CTX-I.

The levels of CTX-I and their distribution among various age groups of study population are shown in Table 1.

Table No.1: Cross tabulation between the age of study group and levels of CTX-I

Age (years)		45	46	47	48	49	50	51	52	53	54	55	Total
Serum CTX (pg/ml)	50-410	17	7	2	6	3	6	2	0	3	0	2	48
	411-920	2	1	3	2	3	3	4	1	0	2	0	21
	921-1230	6	0	2	2	2	6	2	2	2	0	0	24
	1231-1640	1	1	0	1	0	0	1	0	0	0	0	4
	1641-2050	0	1	0	1	1	0	0	0	0	0	0	3
Total		26	10	7	12	9	15	9	3	5	2	2	100

Table No.2: Cross tabulation between the levels of serum CTX-I and grades of Singh index of the study group

Serum CTX-I (pg/ml)	Singh Index			Total
	Grade IV	Grade V	Grade VI	
50-410	0	2	46	48
411-920	0	1	20	21
921-1230	1	6	17	24
1231-1640	0	4	0	4
1641-2050	2	1	0	3
Total	3	14	83	100
P value = 0.000				

The levels of CTX-I and their distribution related to grades of Singh index are depicted in Tables 2 & 3.

The majority of women in this study were taking various medications such as HRT, interleukin inhibitors and food supplements (Table 4).

Table No.3: Cross tabulation between the levels of serum CTX-I and Singh index grades 1-V & V1 of study group

Serum CTX-I (pg/ml)	Singh index		Total
	Grade I-V	Grade VI	
50-410	2	46	48
411-3000	15	37	52
Total	17	83	100
P Value = 0.001			

Table No.4: Cross tabulation between serum CTX-I levels and medications

Serum CTX(pg/ml)	Medication				
	HRT	Interleukin inhibitors	Anti-inflammatory	Supplements	Total
50-410	2	8	1	37	48
411-920	3	2	0	16	21
921-1230	0	2	5	17	24
1231-1640	0	0	3	1	4
1641-2050	0	0	2	1	3
Total	5	12	11	72	100
P Value =0.000					

DISCUSSION

This study was conducted to find out an association between serum CTX-I levels with HRT and interleukin inhibitor therapy. Peri-menopausal women of 45-55 year of age with radiographic evidence of osteoporosis were evaluated in relation to serum CTX-I levels. Singh index was used to provide radiographic evidence of osteoporosis. It was recorded from digital antero-posterior radiographs of pelvis.

Rosen H.N. (2000)[15] described CTX as sensitive marker of bone anti-resorptive therapy and found serum CTX-I levels as sensitive markers of response to treatment.

In a randomized controlled trial, Forsbladd'Elia et al.[16] found that treatment with HRT in postmenopausal women reduced markers of bone turnover. They found that reduction in bone turnover markers was associated with improved bone mass after 2 years, with CTX-I providing the most sensitive prognostic value.

CTX-I is an early indicator of bone degradation as it was increased in grade VI women which shows bone loss without radiological evidence. This is supported by Greenspan et al [17] who described CTX-I as more reliable marker for bone anti-resorptive therapy.

In present study, it was observed that majority of peri-menopausal women were taking various supplements and medications like HRT, interleukin inhibitors, anti-inflammatory drugs.

A significant association (negative correlation) was found between hormone replacement and anti-resorptive therapies and CTX-I levels by applying Chi-square test. (p =0.000).

CONCLUSION

The levels of CTX remain low in patients taking HRT and interleukin inhibitors indicating their protective role in osteoporosis. Thus we conclude from our study that there is a significant association of serum CTX-I levels with both hormone replacement and interleukin inhibitor therapies.

Recommendation: It is recommended that both hormone replacement and interleukin inhibitor therapies should be encouraged in peri-menopausal women.

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

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