ORIGINAL ARTICLE

CYTOKINE AND HORMONAL PROFILE IN OSTEOARTHRITIS SUBJECTS

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ABSTRACT

Objective: To assess whether the hormones and cytokines are linked with postmenopausal osteoarthritis.

Material and Methods: The study comprised of one hundred and fifty patients suffering from OA and one hundred and thirty control groups having the age from 44 to 58 years. Thyroid hormones (T3, T4) , calcitonin, estrogen, progesterone hormones, and Interleukin-6 (IL-6) were analyzed by ELISA

Results: Level of serum estrogen in OA subjects and control subjects were 29.73 ± 4.96 and 51.16 ± 3.11 respectively. (P<0.0001). This value was significantly low in the patients when compared with controls. Patients also show significant high interleukin 6 levels (21.98 ± 0.33) when compared with control subjects 5.4 ± 0.1.9 (P < 0.0001).

Conclusion: It is suggested that estrogen deficiency after menopause is associated with osteoarthritis in postmenopausal women.

Keywords: Postmenopausal, women, Osteoarthritis, hormone.

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INTRODUCTION

Amongest the common chronic diseases, osteoarthritis effect the weight bearing joints. Disease causing gradually and irreversible joint damage[1] . Continuous progressive articular cartilage destruction, pain, inflammation of synovial and other decremental changes of sub-chondral bone are a very clear spectacle of this disease. Pathological changes occur during osteoarthritis, including biomechanical forces produced that lead to imbalance between tissue turnovers within the joints[2]. Various factors play a role in its pathogenesis including biomechanical factors, pro-inflammatory mediators and proteases[3].

In OA, cellular inflammation is not prominent but this inflammatory component is more pronounced at molecular level manifested by presence of pro-inflammatory mediators including cytokines and chemokines. These cytokines and chemokines are responsible for the production of proteases that in turn are responsible for joint destruction and degeneration. Key role is played by an imbalance of pro-inflammatory and anti-inflammatory cytokines[4].

According to study conducted by Zhang Y, this disease affects 15 to 40 % of people who have age over 40 years[5]. The disease reduces the quality of life and is one of the chief reasons of disability of person[6,7]. There are many causes and risk factors for osteoarthritis but obesity, age and deficiency of sex hormones are the major risk among these subjects encountered in clinical practice. Obesity develops the mechanical force between the weight bearing joints that ultimately leads to osteoarthritis.

It affects females more often as compared to males after menopause when sex hormones levels decline[8]. Therefore menopause is associated with the OA in women. Estrogen plays a significant role in bone health[9]. This sex hormone has function to decline the serum calcium and phosphate. According to Dietrich W, patients who were on estrogen replacement therapy have low concentration of calcitonin[10]. Similarly, it was observed that different cytokines are affected when the levels of estrogen are low. Due to deficiency of estro-

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gen, osteoclast precursors become more sensitive to interleukin [6].

In the present study factors related to pathogenesis of osteoarthritis are discussed and as osteoarthritis is a big problem of postmenopausal women so by knowing the factors that are involved in pathogenesis of OA, we can suggest the treatment that can help reducing symptoms and severity of disease and hence can minimize the morbidity. This study is hoped to contribute to already published literature on this topic.

MATERIALS AND METHODS

This cross sectional study was conducted at University of Karachi from 2014 to 2016. Total one hundred and fifty patients (150) suffering from OA and one hundred and thirty (130) control subjects were included in this study. Selection of the patients (44-58 years) was based on sign and symptoms, as well as their history and affected joints. Their radiographs were also taken for the correlation with biochemical parameters. Their radiographs were used to diagnose the disease, as well as to differentiate between their grades. The patients included in this study were of different grades according to their disease severity. Patient exclusion criteria were included the hormonal replacement therapy (HRT) and NSAID users, having metabolic disease, rheumatoid (RA) and SLE positive subjects. Information about their age, gender and others were collected by the questionnaire after informed consent. Controls of this study consisted of 130 subjects having age 46-60 years. All control subjects are age matched with the patients, and having no sign of osteoarthritis. They are postmenopausal women.

We minimized the cofounders like, patients are all postmenopausal women. We exclude the fertile age women to minimize the cofounders. Males are not the part of our study. Blood samples of patients and controls were analyzed for hormones T3 (Kit #: DSL-10-3100S), T4 (Kit#:DSL-10-3200), calcitonin (Kat#:DSL-10-7700), estrogen (Kit#DSL-10-4300), progesterone (Kit # DSL-10-3900) and interleukin 6 (Kat./ Cat#: EIA-3293) by ELISA. All the kits were purchased from Germany.

RESULTS

Demographical data is shown in table-1 for patients and controls. Their age, height, weight and BMI are given in this table. Data of the patients shows no statistical significance when compare with the controls. No obese person was included in the study.

Table-2 shows different hormones levels like triiodothyronin T3, tetraiodothyronin T4, calcitonin, estrogen and progesterone. IL-6 levels in both patients and control group were also mentioned in this table. Estrogen level of the patients group was found significantly low when it compared with control group ($p \leq 0.001$). While level of interleukin-6 of the patients was significantly high as compared to control subjects ($p \leq 0.001$). Correlations between the hormones as well as with IL-6 were also shown through the correlation graphs.(Fig 1,2,3 and 4).Figure number 2 give strong correlation between estrogen and progesterone (Correlation: r =0.1787).But the other figures don't show any significant correlation among other hormones of the study included.

DISCUSSION

Osteoarthritis (OA) is a disease with multi-factorial etiology. Apart from inflammatory cytokines there are several hormones that can have strong association with the development of OA among which most important is

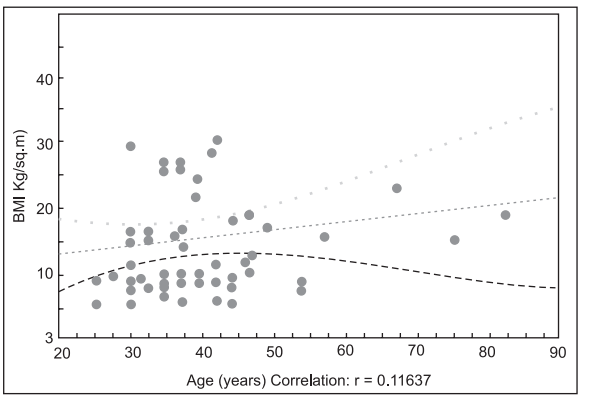

Figure 1: Correlation of Age vs BMI in osteoarthritis patients

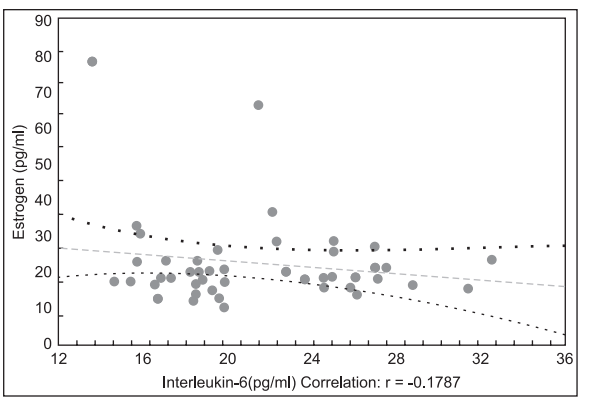

Figure 2: Correlation of Interleukin-6 vs. Estrogen in Osteoarthritis Patients

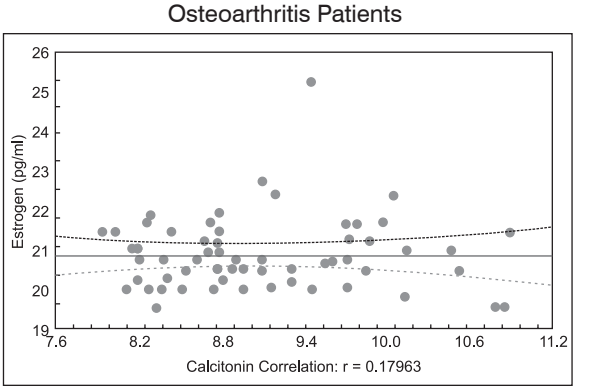

Figure 3: Correlation of Calcitonin Vs Estrogen levels

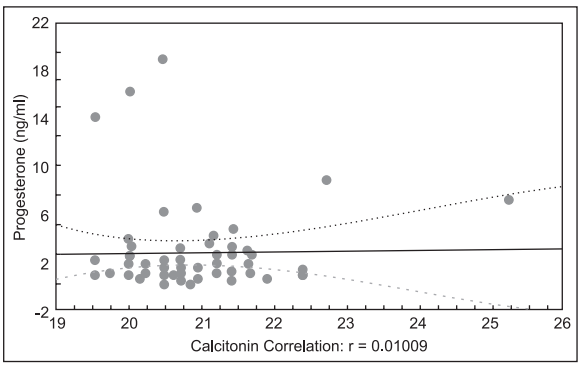

Figure 4: Correlation of Calcitonin vs Progesterone levels

Table 1: Demographic details of control and patients

Variables	Patients	Controls
Age (years)	*51 ± 3.54 (44-58)	53 ± 4.10(46-60)
Height (cm)	159.95± 3.44	161.23±2.51
Weight (kg)	63.54±4.65	60.50±3.87
BMI (kg/ m2)	23.08± 3.22	22.81± 2.19

Values are the mean ± S.E.M.

* p < 0.001 as compared to control subjects

Table 2: Parameters in Control and Osteoarthritic Subjects

Variables	Patients n (150)	Controls n (130)	P – value
T3 (ng/dl)	140 ± 1.44	143± 1.92	< 0.027
T4 (ug/dl)	7.92± 0.31	8.17± 0.28	< 0.045
Calcitonin (pg/dl)	27.84± 0.17	28.71± 0.11	< 0.076
Estrogen (pg/dl)	*29.73±4.96	51.16± 3.11	< 0.001
Progesterone (ng/ml)	3.83±1.23	4.64± 0.89	< 0.013
Interleukin-6(pg/ml)	*21.98±0.33	5.4 ± 0.1.9	< 0.001

Mean + S.E.M are shown.

estrogen. There are several studies that have highlighted the role of estrogen in pathogenesis of OA because of convincing evidences about direct effect of estrogen on joint tissues in human and animal model. Studies found that the effect of estrogen on chondrocytes is very strongly associated with the age of individual, there is significant difference in Estrogen receptor (ER) affinity for its ligand at different ages[11] (Table 1 and Figure 1). OA was considered a deteriorating joint disease later it was accepted that chiefly a complex inflammatory process is involved in its pathogenesis[12,13].

Postmenopausal decline in level of estrogen predisposes female to Osteoarthritis[14] . There is a decrease in bone mineral density related to decline in estrogen level in post-menopausal woman. Epidemiological studies have shown that hormone replacement therapy in postmenopausal woman have significant therapeutic effect on decreasing the risk of developing osteoarthritis as compared to women who are not taking estrogen replacement therapy. Estrogen deficiency leads to increase number, increase activity and decrease apoptosis of osteoclasts[15].

Incidence and prevalence of OA increases with age, so it is very closely related to age [16]. There are several changes that take place in joint with advancing age including thinning or articular cartilage reduced hydration of matrix and altered biochemical properties of joints that increases the brittleness of joints[17]. Apart from these environmental and mechanical factors and genetic factors, inflammatory mediators drive destruction of joints among these inflammatory mediators[18,19]. Early studies were focused on role of IL-6 which was previously thought the main catabolic hormone and it was thought as primary mediator responsible for joint tissue destruction but its role was questioned because the level found in synovial fluid of OA joint is insufficient to cause cartilage destruction other cytokines that are present in a higher level in synovial fluid of OA joint are IL-6, MCP-1 and IP-10. This accords with our results [20] (Table 2 and Figure 2). Bone metabolism is regulated by a balance of osteoblastic and osteoclastic activity. Lower serum estrogen levels in a post-menopausal women disturbed balance estrogen down regulated the expression of IL-6 gene in osteoblast and stromal cells. IL-6 promoter is inhibited by estrogen in absence of a functional ER binding site [21]. We have not found any correlation between the Progesterone, Calcitonin hormones and thyroid hormones with osteoarthritis (Table 2 and Figure 3,4). This finding is also supported by international literature. [22,23]

CONCLUSIONS

Present study concludes that decline of estrogen is strongly correlated with the interleukins in the osteoarthritis patients.

LIMTATIONS

Our study has some limitations. Study includes only female subjects and they are postmenopausal women. Although osteoarthritis disease has so many other factors not only single hormonal deficiency.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Sheikh SI:	Study conception and design Acquisition of data: Analysis and interpretation of data.
Abbas H:	Drafting of manuscript.
Mirza N:	Critical revision.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.