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Correlation between age-related serum follicle stimulating hormone levels and osteoarthritis in postmenopausal women.

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Abstract

Objective: To study the changes of age-related serum Follicle Stimulating Hormone (FSH) level and X-ray of knee joint and the relationship between FSH and postmenopausal knee osteoarthritis in postmenopausal women.

Methods: 248 postmenopausal women aged over 50 y were randomly selected from Shandong Provincial Hospital affiliated with Shandong University after excluding patients with related diseases and medication history that affected bone metabolism and the that long-term used bone metabolism drugs. The levels of serum FSH, Luteinizing Hormone (LH) and Estradiol (E2) were measured by radioimmunoassay, and knee joint by X-ray. The changes of serum FSH, LH, E2 with age were analysed. The difference of FSH level between patients with postmenopausal osteoarthritis and control group was compared.

Results: The serum FSH and LH levels increased with age, reaching a peak around 60 y old, and then decreased with age. Serum E2 levels decreased with age after menopause. Serum FSH and LH levels in patients with knee osteoarthritis were significantly higher than those in the control group (P<0.05), while E2 was significantly lower (P<0.05).

Conclusion: This work shows the changes of FSH, LH and E2 in the postmenopausal women and indicates that FSH level may have an effect on the development of osteoarthritis.

Keywords: FSH, Osteoarthritis, Menopause.

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Introduction

In recent years, the incidence of Knee Osteoarthritis (KOA), also known as degenerative arthritis, has been increasing year by year. Epidemiological survey found an Osteoarthritis (OA) prevalence of 66% [1,2]. Therefore, the etiology and pathogenesis of OA has become a hotspot in recent years. OA pathogenesis is not yet clear. Occurrence and development of OA in the endocrine system dysfunction has been paid more and more attention [3,4]. Studies have shown that estrogen can be combined with estrogen receptors on the chondrocytes to promote cartilage cells to secrete a variety of collagenase and growth factors, enhancing the function of chondrocytes and promoting cartilage formation. At the same time, inhibiting the Interleukin-1 (IL-1) and Interleukin-6 (IL-6), results in reduction of the destruction of articular cartilage by inflammatory reaction. In recent years, the findings of new research challenge this view. Sun et al. [5] found that through the Tumor Necrosis Factor-Q (TNF-Q), Follicle Stimulating Hormone (FSH) can improve levels of inflammatory cytokines such as IL-6 and Interleukin-8 (IL-8), direct inhibiting cartilage synthesis without affecting estrogen concentration. Xu et al. [6] found that female serum FSH concentration has positive correlation with level of bone turnover markers. Richard et al suggested that LH and FSH changes with age, specifically age-associated increases [7]. Serum FSH level increases in perimenopausal women, and serum FSH changes have a better indication of the destruction of cartilage cells than estrogen and androgen. The study also found that, for amenorrhea patients caused by excessive secretion of FSH, chondrocyte shows significantly decreased synthesis and increased damage. These results suggest that FSH may be a regulator of bone mass.

To further understand the changes of serum gonadotropin and sex hormones in postmenopausal women and the relationship with postmenopausal OA, especially KOA, we measured 248 postmenopausal women over 50 y old by radioimmunoassay. FSH, Luteinizing Hormone (LH) and Estradiol (E2) were measured by X-ray, and their bilateral knee joints were examined with Kellgren-Lawrence (KL) grading, The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAS) and T2-mapping of knee joint.

Materials and Methods

Subjects

From December 2009 to December 2014 in our hospital for orthopedic treatment, 128 postmenopausal OA patients aged over 50 were randomly selected as the object of study. At the same time, 120 postmenopausal healthy women aged over 50 were selected as control group.

KOA diagnostic criteria

Reference to KOA diagnostic criteria by World Health Organization (WHO) [8]: 1, knee pain during the most time of last month. 2. Bone friction sound. 3. Morning stiffness<30 min. 4. Age ≥ 38 y. 5. Osteogenic hypertrophy. Meeting 1-4 or 1, 2, 5 or 1, 4, 5 can be diagnosed as KOA.

Exclusion criteria

1. Combination with other serious chronic diseases; 2. Combination with diseases of liver, kidney, bone and joint or other endocrine diseases; 3. Perennial taking hormones and bone metabolism drugs (such as glucocorticoids, estrogen, thyroid hormone, calcitonin, diphosphate preparations, calcium, vitamin D, immunosuppressive agents, etc.); 4. Non-natural menopause (uterine and bilateral annex excision).

Determination of FSH, LH, E2

Fasting venous blood was collected from all subjects (7-9 o'clock in the morning). The serum was separated within 1 h and placed in -80°C. The detection of FSH, LH, and E2 was carried out in strict accordance with the instructions of the ELISA kit (R & D, USA).

Statistical analysis

IBM SPSS 17.0 software was used for statistical analysis of data. All measurement data were recorded as $\bar{x} \pm s$, and χ^2 test was used for count. The differences between the groups were analysed by t test, one-way ANOVA and SNK-q test. The correlation analysis was performed by Spearman rank correlation analysis and multivariate analysis by binary logistic regression analysis. It was considered as statistically significant when $P < 0.05$.

Results

General clinical features

In this study, 248 postmenopausal women aged over 50 y in Shandong province were investigated, including 128 KOA patients and 120 healthy subjects. Table 1 shows the number of subjects, height, weight, body mass index and other basic information in each age group.

Serum FSH, LH and E2 levels

The serum FSH and LH levels increased with age, reaching a peak around 60 y old, and then decreased with age. Serum E2 levels decreased with age after menopause (Table 2).

Comparison of serum FSH, LH and E2 levels in postmenopausal women with KOA and the control

The results showed that serum FSH and LH levels in KOA patients were significantly higher than those in the control group ($P<0.05$), but E2 levels were significantly lower ($P<0.05$, Table 3).

Table 1. *General clinical characteristics of subjects in each age group.*

Characteristics	50-54 (n=65)	55-59 (n=63)	60-64 (n=59)	≥ 65 (n=61)	F	P
Height (cm)	159.13 ± 5.17	159.54 ± 4.79	156.92 ± 5.67	156.92 ± 5.67	0.291	0.832
Weight (kg)	61.38 ± 9.09	64.10 ± 8.52	63.55 ± 9.54	66.29 ± 10.38	2.902	0.036
BMI (kg/m^2)	24.22 ± 3.22	25.22 ± 3.54	25.76 ± 3.21	27.15 ± 4.19	7.381	0.001

Table 2. *Serum FSH, LH and E2 levels of the subjects in each age group.*

Factors	50-54 (n=65)	55-59 (n=63)	60-64 (n=59)	≥ 65 (n=61)	F	P
FSH (mIU/ml)	51.24 ± 6.52	57.13 ± 4.26*	56.93 ± 6.08*	48.75 ± 4.48*	36.545	0.001
LH (mIU/ml)	50.50 ± 4.53	54.41 ± 3.71*	53.85 ± 4.82*	47.03 ± 3.39*	41.446	0.001
E2 (pg/ml)	11.71 ± 2.51	8.96 ± 2.59*	7.41 ± 2.04*	6.25 ± 1.91*	67.182	0.001

Note: *compared with the 50-54 age group, P<0.05.

Table 3. *Comparison of serum FSH, LH and E2 Levels in postmenopausal women with KOA and the control.*

Age	n	FSH (mIU/ml)	LH (mIU/ml)	E2 (pg/ml)

		Control group	KOA group	Control group	KOA group	Control group	KOA group
50-54	65	49.26 ± 6.09	53.28 ± 6.42*	48.51 ± 4.29	52.51 ± 3.87*	12.93 ± 2.20	10.46 ± 2.19*
55-59	63	55.13 ± 4.49	58.95 ± 4.73*	53.36 ± 3.20	55.36 ± 3.94*	9.73 ± 2.51	8.26 ± 2.79*
60-64	59	54.96 ± 5.69	58.70 ± 5.96*	52.42 ± 5.05	55.14 ± 4.29*	8.06 ± 2.15	6.81 ± 1.77*
≥65	61	47.22 ± 4.32	50.14 ± 4.92*	45.36 ± 3.80	48.54 ± 3.44*	6.45 ± 2.02	6.06 ± 1.81*

Note: *Compared with control group at the same age, P<0.05.

Discussion

As the average life expectancy increases and the population structure changes, OA has become a global public health problem. According to the International OA Foundation statistics, the global OA patients was about 200 million in 2008, seriously endangering the health and life quality of the elderly. Postmenopausal OA was common in postmenopausal women, mostly with the age over 50 y old, showing rapid degeneration of cartilage, secondary bone hyperplasia, and reduced synovial fluid. At present, the exact mechanism of postmenopausal OA is not entirely clear. We only know that degenerated articular cartilage results in secondary osteoarthritis, leading to OA occurrence. The traditional view was that estrogen deficiency in postmenopausal women was the direct cause of OA. Due to decreased levels of estrogen, cartilage destruction was stronger than the cartilage formation, leading to accelerated cartilage reduction, eventually leading to OA. In recent years, several new studies have revealed that FSH played an important role in the regulation of chondrocyte metabolism.

FSH is a hypothalamic-pituitary axis glycoprotein hormone composed by anterior pituitary cells and basophils. For women, FSH can contribute to the growth of the endometrium, ovulation induction and follicular development. While for men, FSH can promote the sperm production. FSH specifically binds to FSH receptor cells (FSHR), and then initiates intracellular signaling, which plays an important biological role. For women, FSH binds to the FSHR as indicated by granulosa cell membranes, and regulates cell proliferation and differentiation by intracellular cyclic AMP/PK pathway, resulting in estrogen production. It played a key regulatory role in the follicle formation, development and maturation process. For men, FSH mainly promotes sperm formation through the regulation of testicular support cells.

FSH regulating OA was a hot spot in the pathogenesis study of postmenopausal OA. Early studies have shown that serum FSH and chondrocyte proliferation were negatively correlated. In this way, FSH could be used to predict chondrocyte apoptosis. Amenorrhea occurrence was the result of excessive secretion of FSH and reduced estrogen. FSH can be directly involved in the regulation of chondrocytes. The results of this study showed that the serum FSH and LH levels were significantly increased in the 50 y old postmenopausal women, peaked in the 60-64 age group, and then decreased, other studies also suggest similar gonadotropin (FSH and LH) responses to aging [9,10].

In addition, the results of this study also found that serum levels of FSH and LH in postmenopausal patients were higher than those in the control subjects group of same age, indicating that FSH could be related to the loss of chondrocytes, which was consistent with some other studies [11,12]. Foreign scholars found that chondrocytes of FSHR knockout mice did not decrease although with increased FSH levels, indicating that FSH and gonadal dysfunction caused by chondrocyte reduction were closely related. Further studies showed that FSHR gene knockout male mice had no reduction in chondrocytes, except for hypogonadism. There's no significant difference comparing chondrocytes density and wild-type control group. Further studies have shown that mice lacking the FSHR beta subunit had normal levels of estrogen compared to the wild type, but serum TRAP, cathepsin K, and other factors associated with chondrocytes were significantly reduced. Besides, OPG and other cartilage formation index did not change significantly. Therefore, for the mice with normal estrogen levels, the maintenance of the number of chondrocytes was not caused by the increase in chondrocytes, but by the decreased serum FSH levels, reducing chondrocyte apoptosis, thereby increasing the cartilage cells. This also demonstrated the direct effect of FSH on cartilage metabolism. *In vitro* studies have shown that FSH could be directly involved in the regulation of the number of chondrocytes. FSH had no effect on the development of chondrocytes, but FSH could stimulate immune cells to produce TNF-Q, promoting chondrocyte apoptosis and death [13-18].

Above all, the conclusion we can draw from the research is the FSH, LH and E2 value of KOA patients from postmenopausal women changed, and FSH level may have an effect on the development of osteoarthritis.

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