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The relationship between *IL-17* gene polymorphism and osteoporosis in postmenopausal women: A meta-analysis.

Jiefu Song*, Zhizhen Jin, Feng Chang, Lijun Li, Yunxing Su

Department of Orthopedics, Shanxi People's Hospital of Taiyuan city of Shanxi Province, Taiyuan, PR China

Abstract

Objective: To investigate the relationship between Interleukin -17 (*IL-17*) gene polymorphism and Osteoporosis (OP) in postmenopausal women.

Methods: The domestic and foreign related research (Before June 2017) published *IL-17* gene polymorphism and postmenopausal osteoporosis were given searching. All the literature was given meta-analysis, and were calculated the index for the literature merge effect.

Results: A total of 10 case-control studies discovered, the comparisons of *IL-17* C2/2, C4/4, C2/3, C2/4 genotype and C2 allele between the post-menopausal OP group and control group showed no significant heterogeneity (χ^2=1.294, 0.873, 0.911, 1.004 respectively, all P>0.05), and the comparisons of *IL-17* C3/3, C3/4 genotypes and C2, C3, C4 in different studies had significant heterogeneity (χ^2=6.954, 5.211, 8.144, 6.104, 4.209, all P<0.05). Odd Ratios (OR) of *IL-17* C2/2, C3/3, C4/4, C2/3, C2/4, C3/4 genotypes in post-menopausal OP group were 0.855, 0.554, 2.721, 0.816, 1.793 and 2.330 respectively. Fix effect model and random effect model showed that the data of *IL-17* genotypes and alleles distribution in post-menopausal OP patients were in accordance with OR and its P value.

Conclusion: The *IL-17* C2/4, C4/4 C 3/4 genotypes and C4 allele may be susceptible genetic risk factors for postmenopausal OP.

Keywords: Postmenopausal women, *IL-17*, Gene polymorphism, Osteoporosis, Meta-analysis.

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Introduction

Osteoporosis (OP) is characterized by a decrease in bone mass as well as a deterioration of the bone architecture, tends to afflict elderly, while women menopause factors more prone to osteoporosis [1,2]. Epidemiological surveys show that OP affects about one-third of postmenopausal women, leading to complications such as constipation, venous thrombosis and pneumonia [3,4]. The pathogen of postmenopausal OP mainly results from estrogen levels decline, research shows that lack of estrogen can also enhance the strength of bone remodeling, but estrogen lead to bone resorption phenomenon is dominant [5,6]. Modern studies demonstrated that postmenopausal OP is an autoimmune and inflammatory process, and T cells play a major role in this process [7]. Interleukin-17 (*IL-17*) is characteristic cytokines of $CD4^+$ cells and the group of Th17 cells secrete, the lack of estrogen will lead to increased Th17 cell differentiation, showed that *IL-17* plays an important role in the formation of osteoclast [8]. At present, gene polymorphism has been extensively studied in clinical medicine, and its relationship with susceptibility to disease has gradually increased. However, due to age difference in gene polymorphisms, the incidence of various diseases in different age groups is very different. The population, *IL-17* has three IL-17 alleles and six genotypes. Thus constituting gene polymorphism [9]. However, the current study included a relatively small sample size, and a larger sample size was required to determine the distribution characteristics of post-menopausal OP patients and *IL-17* genes [10]. Meta-analysis is a method to estimate a "common" curative effect, the "average" comprehensive statistical, and a basic statistical method for the systematic evaluation of literature by evidence-based medicine. To improve test efficiency, by studying as much as possible for the same purpose of independent research literature [11]. This study systematically evaluated the relationship between *IL-17* gene polymorphism and postmenopausal OP.

Materials and Methods

Inclusion and exclusion criteria

Inclusive criteria: 1. case-control study before June 2017; 2. initial data; 3. provide sufficient data to calculate the size of an effect value; 4. postmenopausal women with osteoporosis; 5. large sample size (≥ 60 samples).

Exclusive criteria: 1. diagnose patient without clear; 2. repeated reports, poor quality of research and incomplete documentation.

Document retrieval

The EMBASE, PubMed and MEDLINE literature database were used to retrieve the English full-text, and the Chinese full-texts were by using Wanfang database and CNKI. When searching, the keywords in Chinese were "interleukin-17", "*IL-17*", "gene polymorphism", "postmenopausal osteoporosis" and "osteoporosis". The keywords in English were "*IL-17*", "gene polymorphism", and "osteoporosis". The literatures were retrieved before June 2017.

In the process of retrieval, literatures screening followed the literature inclusion and exclusion criteria of this study strictly. The literature materials related to this study were extracted, and references were analysed by the retrospective analysis. The process was carried out by two independent evaluators respectively, and they reached the consensus, in order to avoid missing any reference to the standard. All analyses in this study were based on previous published studies, the ethical characteristics of this study were met for the ethical requirement.

Research quality evaluation

Evaluation by using the method of the Q statistic test heterogeneity between the research object, through the application of the Cochrane collaboration methods to evaluate the quality, plotting funnel figure. If funnel figure basically were distribution symmetrically, publication bias will be small.

Statistic treatment

The Review6.0 software was selected for statistical analysis of the included data, and all statistical analysis results were characterized by $P<0.05$. The genotype distribution was analysed by the Hardy-Weinberg balance law, and the distribution of genotype and allele frequency distribution of the two groups was analysed using the R × C card. Measurement data was expressed as $\bar{x} \pm s$, comparison between the two groups using independent sample t test, multiple sets of comparison between the One-Way ANOVA. Classification variable data were described by the composition ratio, and the chi-square test was adopted in the comparison between groups. Heterogeneity test: $P<0.05$, select the random utility model; $P>0.05$, select the fixed utility model. By means of statistical analysis of statistical analysis, the influence of the publication bias on the meta-analysis was included in the paper.

Results

Literature inclusion

The literature has been retrieved 35 relevant literatures and abstracts were checked, including 18 articles, 5 articles from the non-mainstream literature magazine which did not reach the standard, 1 article due to unclear definition in control group or abnormal people as control from the exclusion criteria, 2 articles due to no sufficient research data from the exclusion criteria. At last, 10 study literatures were included, there were 451 cases in the postmenopausal OP group and 561 cases in the control group [1-10]. The results are shown in Figure 1.

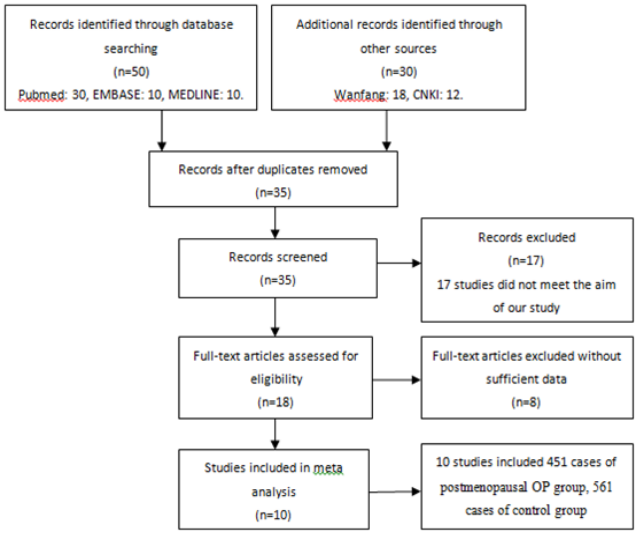

Figure 1. *The literature selection and inclusion process.*

Heterogeneity test

The genotype of C2 allele and *IL-17* C2/2, C2/3, C4/4 and C2/4 genotypes were compared in the post-menopausal OP group and the control group, and the heterogeneity was not significant ($P>0.05$). The heterogeneity between *IL-17* C3/4, C3/3 genotypes and C2, C3, C4 was quiet different ($P<0.05$, Table 1).

Table 1. *IL-17 gene polymorphism and heterogeneity test of postmenopausal OP.*

IL-17 gene polymorphism	χ^2	P
IL-17 C2	8.144	<0.05
IL-17 C3	6.104	<0.05
IL-17 C4	4.209	<0.05
IL-17 C2/2	1.294	>0.05
IL-17 C4/4	0.873	>0.05
IL-17 C2/3	0.911	>0.05
IL-17 C2/4	1.004	>0.05
IL-17 C3/4	5.211	<0.05
IL-17 C3/3	6.954	<0.05

Meta-analysis

The OR of *IL-17* C2/2, C4/4, C3/3, C2/3, C3/4, and C2/4 in the postmenopausal OP group was 0.855, 2.721, 0.554, 0.816, 2.330 and 1.793 (Table 2). The funnel plot was showed in Figure 2.

Table 2. *IL-17 gene polymorphism and meta-analysis of postmenopausal OP.*

IL-17 gene polymorphism	OR	95% CI
IL-17 C2/2	0.855	0.470~1.553
IL-17 C3/3	0.554	0.430~0.782
IL-17 C4/4	2.721	1.632~4.561
IL-17 C2/3	0.816	0.661~0.982
IL-17 C2/4	1.793	1.124~2.671
IL-17 C3/4	2.330	1.753~3.109

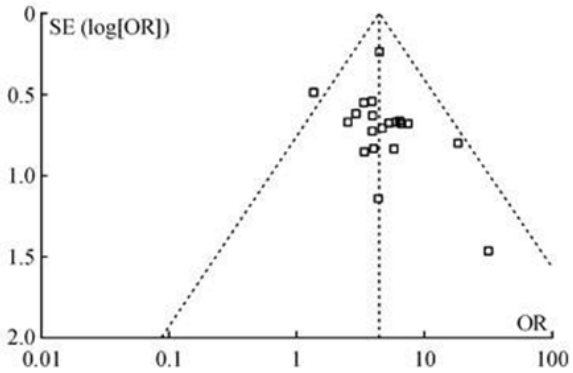

Figure 2. *IL-17 gene polymorphism and the meta-analysis of funnel plot of postmenopausal OP.*

Sensitivity analysis

By utilizing the fix effect model and random effect model for post-menopause OP patients were used for combining with of IL-17 genotype and allele distribution data merging, the merger of the two models OR almost the same value with the corresponding P, meta-analysis result has a good reliability (Table 3). The forest chart was showed in Figure 3.

Table 3. *Sensitivity test of IL-17 gene polymorphism and meta-analysis of postmenopausal OP.*

IL-17 gene polymorphism	Fixed effect model		Random effect model	
	OR	P	OR	P
IL-17 C2	0.915	0.264	0.924	0.482
IL-17 C3	0.664	0	0.652	0
IL-17 C4	2.201	0	2.441	0
IL-17 C2/2	0.851	0.692	0.784	0.489
IL-17 C3/3	0.644	0	0.562	0
IL-17 C4/4	2.671	0.002	2.441	0.002
IL-17 C2/3	0.842	0.031	0.824	0.051
IL-17 C2/4	1.794	0.017	1.762	0.022
IL-17 C3/4	2.104	0	2.443	0

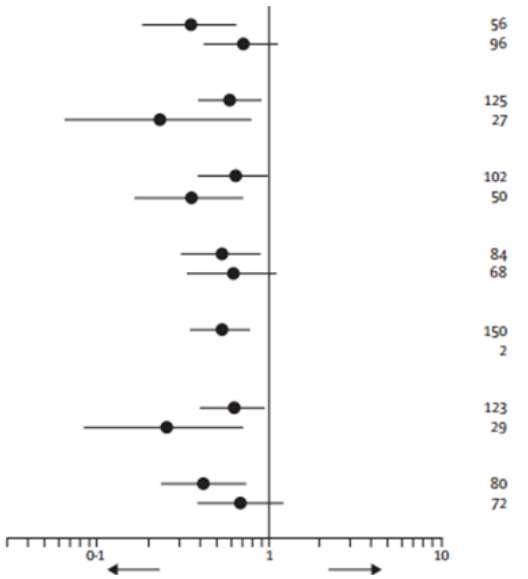

Figure 3. *IL-17 gene polymorphism and the meta-analysis of funnel plot of postmenopausal OP.*

Discussion

Osteoporosis is characterized by a decrease in bone mass as well as a deterioration of the bone architecture resulting in an increased risk of fracture [12]. After the menopause, due to low estrogen level, the imbalance of bone coupling process causes the decrease of bone mass, which can lead to the occurrence of OP. Modern research suggests that the etiology of the postmenopausal OP is complex, postmenopausal OP in identical twins and first-degree relatives of incidence of a disease is significantly higher than normal people, and show the characteristics of its incidence decreased obviously, and closely related to the environmental factors, genetic factors, therefore for the molecular biology research are also being carried out [13,14].

Proinflammatory cytokines such as Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) have turned out to be involved in the pathogenesis of osteoporosis [15]. *IL-17* is $CD4^+$ cells and the characteristic of a group of Th17 cells secrete factors that can work together with TNF-α enhance the process of the development of inflammation and bone transformation [16]. Some scholars believe that the polymorphism shown in *IL-17* has an effect on the bone density of young and old women, and genetic factors play a key role in determining bone mass [17]. As a statistical method, the results of meta-analysis as the best evidence can better solve the inconsistencies of the research results and play an important role in clinical decision-making. Meta-analysis of this study showed that *IL-17* C2/2, C4/4, C2/3, C2/4 C2 allele and genotype in postmenopausal OP without heterogeneity between group and the control group (P>0.05), and *IL-17* CC3/4, 3/3 genotype and C4 and C3 heterogeneity between different research is significant

($P<0.05$). It is demonstrated that *IL-17* C3 and *IL-17* C4 are one of the main pathogenic factors of postmenopausal OP.

The condition of bone turner can be controlled by *IL-17 via* the products of various inflammatory cells, including chemokines and cytokines. Some study found that in young women, the bone density of the lumbar, body and femoral neck was much lower than that of women with the genotype of C4/4 or C2/2 [18]. In older women, the bone density of the whole body and the lumbar vertebra, the female of genotype C4/4 was considerably lower than that of the genotype of C3/3 [19,20]. Previous report studied that the transforming growth factor polymorphisms might be susceptibility to postmenopausal OP [21]. On this basis, this study reports that *IL-17* C2/2, c4/4, C3/3, C2/3, C3/4, C2/4, the corresponding OR values of ischemic stroke are 0.855, 0.554, 2.721, 0.816, 1.793 and 2.330. The combination OR value of *IL-17* genotype and allele distribution data is basically consistent with the corresponding P value, and the results of meta-analysis are more reliable. *IL-17* C2/3 and *IL-17* C3/3 genotypes are protective factors after menopause, *IL-17* C3/4, *IL-17* C4/4, *IL-17* C2/4 are the risk factor for postmenopausal OP, while *IL-17* C2/2 genotype has no correlation with postmenopausal OP. Meta-analysis also has certain limitations: limitations of research conditions. Some related literatures may not be included; the source literatures are convenient to sample. Publication bias is unavoidable in the absence of grey literature. In the future, more empirical papers will be published to verify the results of this meta-analysis and enhance the stability and credibility of the results [22-27].

In conclusion, the C4 allele and *IL-17* C4/4, *IL-17* C2/4, *IL-17* C3/4 genotype may be the risk of postmenopausal OP and genetic susceptibility factors.

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*Correspondence to

Jiefu Song

Department of Orthopedics

Shanxi People's Hospital of Taiyuan city of Shanxi Province

PR China