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Original Article

Effect of interleukin-6 polymorphism on fracture risk

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Abstract: Background: Interleukin-6 (IL6) -174C/G polymorphism was suggested to be associated with fracture risk. However, the results were inconsistent. Thus, we did a meta-analysis. Methods: Reported studies were searched from online electronic databases of Pubmed, EMBASE, Chinese National Knowledge Infrastructure (CNKI). The odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated to assess the association between *IL6* -174C/G polymorphism and fracture risk. Results: Six studies evaluated the association between *IL6* -174C/G polymorphism and fracture risk. A significant association was found between *IL6* -174C/G polymorphism and fracture risk (OR=1.25; 95% CI, 1.10-1.43; *P*=0.0008). In the subgroup analysis of gender, we found that women with *IL6* -174C/G polymorphism had an increased fracture risk (OR=1.25; 95% CI, 1.07-1.46; *P*=0.005). In the subgroup analysis of type of fracture, we found that *IL6* -174C/G polymorphism was significantly associated with wrist fracture (OR=1.25; 95% CI, 1.07-1.47; *P*=0.006) and osteoporotic fracture (OR=1.60; 95% CI, 1.12-2.28; *P*=0.009). However, no significant association was found between *IL6* -174C/G polymorphism and hip fracture (OR=1.05; 95% CI, 0.89-1.24; *P*=0.53) and stress fracture (OR=1.25; 95% CI, 0.97-1.61; *P*=0.08). Conclusion: This meta-analysis suggested that the *IL6* -174C/G polymorphism was associated with wrist and osteoporotic fracture risk.

Keywords: Fracture, interleukin-6, genetics

Introduction

Fracture, most prevalent in elderly women with low bone strength, was an important cause of increased mortality and morbidity [1]. The survivors of fracture often had impaired quality of life [2]. The costs of fracture in Europe were estimated to be about 36 billion Euros per year [3].

Inflammation played an important role in the development of fracture. Estrogen normally suppressed the production of interleukin 6 (IL-6) [4]. The decline in estrogen production after menopause lead to increased IL-6 production. Thus, increased IL-6 in the bone microenvironment lead to the differentiation of osteoclast precursor cells into mature osteoclasts, and increased bone resorption [5]. Additionally, Beeton et al. suggested that the serum level of IL-6 was significantly higher in patients with fracture compared with the control group [6]. Genetic factors also played critical roles in the pathomechanism of fracture [7]. Some previous studies reported the association between *IL6* -174C/G polymorphism and fracture risk [8-13]. However, the results were inconsistent. Therefore, a meta-analysis of *IL6* -174C/G polymorphism and fracture risk was carried out.

Methods

Search studies

Reported studies were searched from online electronic databases of Pubmed, EMBASE, Chinese National Knowledge Infrastructure (CNKI) (Last search was updated on October, 2014). The search terms were used as follows: ("interleukin-6" or IL6 or IL-6) and ("fracture" or "bone fracture" or "fracture, bone") and ("polymorphism" or "genetic"). We also identified the reference lists of all retrieved articles and relevant reviews. No language restriction was used.

Inclusion criteria

The following criteria were used: (1) a case-control study or cohort study assessed the association between *IL6* -174C/G polymorphism and fracture risk; (2) sufficient data were available for calculation odds ratios (OR) and 95% confi-

Table 1. Characteristics of included studies

Author	Year	Country	Ethnicity	Age	Female (%)	Sample size
Nordstrom	2004	Sweden	Caucasian	75±0	100	964
Moffett	2004	USA	Caucasian	73±5	100	1546
Dinçel	2008	Turkey	Caucasian	74±9	62	37
Breuil	2009	France	Caucasian	70±7	100	161
Korvala	2010	Finland	Caucasian	20±2	NA	192
Yanovich	2012	Israel	Caucasian	20±2	NA	385

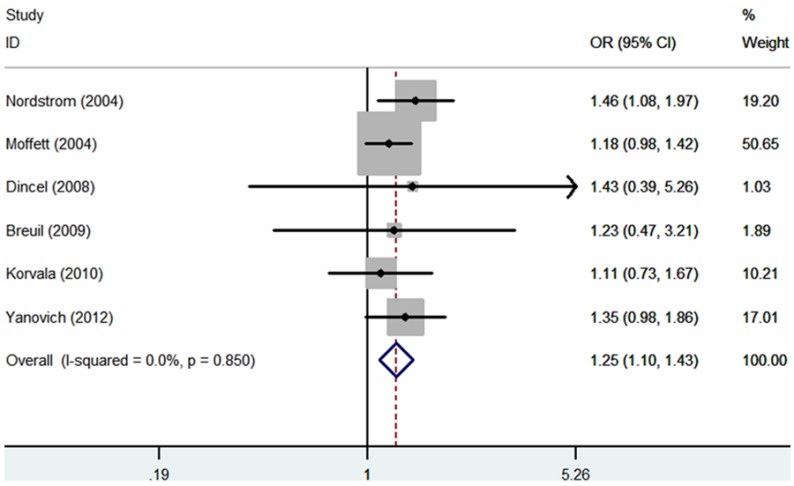

Figure 1. Forest plot for the association between *IL6* -174C/G polymorphism and fracture risk.

dence interval (CI). Only studies meet these criteria at the same time would be included for analysis.

Data extraction

Data was extracted from the eligible studies by two authors independently. The following data were extracted: the first author, publication year, country, ethnicity, age, number of subjects. We contacted the authors if more data were needed.

Statistical analysis

The OR and corresponding 95% CI were calculated to assess the association between *IL6* -174C/G polymorphism and fracture risk in dominant model. The heterogeneity was calculated by Chi square-based Q test and I^2. If no significant heterogeneity was observed, fixed-effects model was used. However, if significant heterogeneity wasobserved, random-effects model was used. Subgroup analysis was done on gender and type of fracture. Publication bias was calculated by Begg's test and funnel plot. Statistical analysis was conducted using Stata software 11.0 (StataCorp, College Station, Texas, USA). A *P*-value of <0.05 was considered significant.

Results

Characteristics of studies

A total of six studies with 3285 subjects were included in this meta-analysis. All the eligible studies were performed from 2004 to 2012. Four studies used old populations and two studies used young populations. Three studies included postmenopausal women. The characteristics of the included studies were shown in **Table 1**.

Meta-analysis results

Six studies evaluated the association between *IL6* -174C/G polymorphism and fracture risk. A significant association was found between *IL6* -174C/G polymorphism and fracture risk (OR=1.25; 95% CI, 1.10-1.43; *P*=0.0008; **Figure 1**). Results of this meta-analysis are listed in **Table 2**. In the subgroup analysis of gender, we found that women with *IL6* -174C/G polymorphism had an increased fracture risk (OR=1.25; 95% CI, 1.07-1.46; *P*=0.005). In the subgroup analysis of type of fracture, we found that *IL6* -174C/G polymorphism was significantly associated with wrist fracture (OR=1.25; 95% CI, 1.07-1.47; *P*=0.006) and osteoporotic fracture (OR=1.60; 95% CI, 1.12-2.28; *P*=0.009). However, no significant association was found between *IL6* -174C/G polymorphism and hip fracture (OR=1.05; 95% CI, 0.89-1.24; *P*=0.53) and stress fracture (OR=1.25; 95% CI, 0.97-1.61; *P*=0.08). Funnel plot showed no obvious publication bias (**Figure 2**) and Egger's test also did not suggest significant publication bias (*P*=0.67).

Table 2. Summary of the meta-analysis results

		OR (95% CI)	*P*	$P_{heterogeneity}$
GG+GC vs. CC	Overall	1.25 (1.10-1.43)	0.0008	0.85
GG+GC vs. CC	Female	1.25 (1.07-1.46)	0.005	0.50
GG+GC vs. CC	Hip	1.05 (0.89-1.24)	0.53	0.28
GG+GC vs. CC	Wrist	1.25 (1.07-1.47)	0.006	0.22
GG+GC vs. CC	Osteoporotic	1.60 (1.12-2.28)	0.009	0.56
GG+GC vs. CC	Stress	1.25 (0.97-1.61)	0.08	0.45

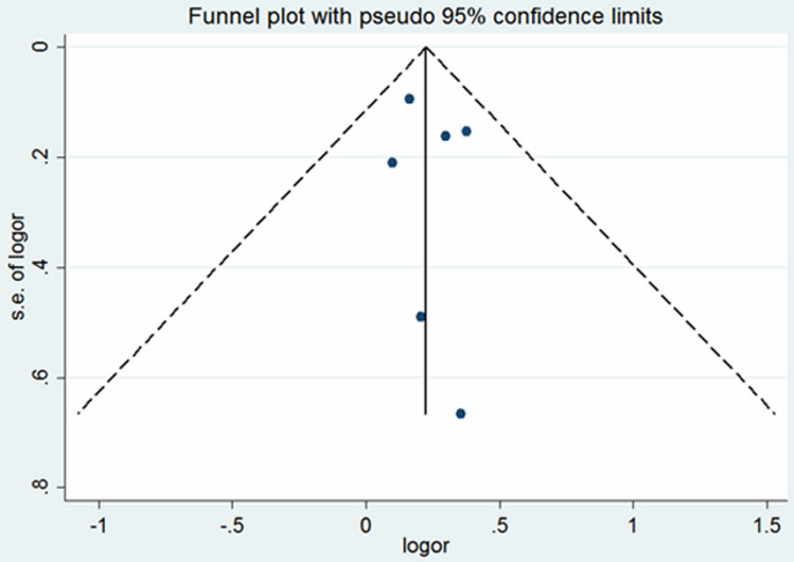

Figure 2. Funnel plot for the publication bias.

Discussion

Although some studies investigated the association between the *IL6* -174C/G polymorphism and fracture risk, the definite conclusion still cannot be addressed. Therefore, we performed this meta-analysis to estimate the relationships between *IL6* -174C/G polymorphism and fracture risk. The meta-analysis involved 6 articles and results from this meta-analysis suggested that the *IL6* -174C/G polymorphism might be a risk factor for fracture, especially in women, wrist fracture, and osteoporotic fracture. To the best of our knowledge, this was the first meta-analysis of the association between the *IL6* -174C/G polymorphism and fracture risk.

The *IL6* -174C/G polymorphism located in the promoter region of the *IL-6* gene. The G allele-was reported to be associated with increased promoter activity and plasma IL-6 levels [14]. Lorentzon et al. found that this polymorphism was an independent predictor of bone mineral density (BMD) during late puberty and of peak bone mass in healthy white men [15]. Ferrari et al. suggested that the CC genotype was associated with lower bone resorption and lesser decrease in bone mass in older postmenopausal women [16].

Our meta-analysis had several strengths. First, it was the first meta-analysis which assessed the association between *IL6* -174C/G polymorphism and fracture risk. Second, we have followed the inclusion criteria strictly to reduce possible selection bias. Third, Egger's test and funnel plot were used to assess publication bias. Fourth, the impact of different genetic background was minimized, because all included studies were performed with Caucasians.

Some limitations should also be addressed. First, the number of included studies was small. More studies are needed to further assess the association between *IL6* -174C/G polymorphism and fracture risk. Second, lacking of the original data of included studies limited the evaluation of the effects of the gene-environment and gene-gene interactions in fracture development. Third, we cannot exclude the possibility of undetected bias.

This meta-analysis suggested that the *IL6* -174C/G polymorphism may be associated with wrist and osteoporotic fracture risk. Further studies with a larger sample size are needed to further validate our results.

Disclosure of conflict of interest

None.

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