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Original Article

Association between TGF-β1 +869C/T polymorphism and fracture risk: a meta-analysis

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Abstract: The association between *TGF-β1* +869C/T polymorphism and risk of fractures remained controversial. Therefore, we performed this meta-analysis to investigate this association. We searched PubMed, EMBASE, and Wangfang databases for studies before Aug 2014. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to calculate the strength of association. A total of ten studies were included in this meta-analysis. *TGF-β1* +869C/T polymorphism was associated with a significantly increased risk of fracture (OR=1.41; 95% CI, 1.20-1.65; I^2=0%). In the subgroup analysis according to gender, women was significantly associated with risk of fracture (OR=1.44; 95% CI, 1.20-1.73; I^2=4%). In the subgroup analysis by race, Asians (OR=1.43; 95% CI, 1.06-1.92; I^2=0%) and Caucasians (OR=1.44; 95% CI, 1.13-1.85; I^2=15%) showed increased fracture risk. Our meta-analysis suggested that the *TGF-β1* +869C/T polymorphism may be a risk factor for developing fracture.

Keywords: Fracture, TGF-β1, meta-analysis, polymorphism

Introduction

Fractures are one of the most common causes of disability and a major contributor to costs of medical care in all regions of the world [1]. Clinical consequences of fracture include short and long-term morbidity characterized by pain, limitation of function, decreased health-related quality of life, and increased mortality. As fracture prevalence increases in tandem with increasing longevity of the population osteoporosis is becoming an even more significant public health burden [2].

Transforming growth factor (TGF)-β is a multiplicity factor mediating cellular processes, including cell growth, cell differentiation, apoptosis, and cellular homeostasis [3]. *TGF-β1* knockout mice display reduced BMD and bone elasticity [4]. Furthermore, Camurati-Engelmann disease, an autosomal dominant, progressive diaphyseal dysplasia, characterized by hyperostosis and sclerosis of the diaphyses of long bones, is caused by mutations in the *TGF-β1* gene [5]. Thus, *TGF-β1* might play an important role in the fractures.

The human *TGF-β1* gene is located on chromosome 19q13.1-13.39. Some studies have investigated the associations between the *TGF-β1* +869C/Tpolymorphism and susceptibility of fractures [6-15]. However, the association between this polymorphism and the risk for fractures was controversial and inconclusive. This meta-analysis aimed to explore the association between the *TGF-β1* +869C/T polymorphism and risk of fractures.

Methods

Publication search

Online electronic databases (PubMed, EMBASE, and Wanfang database) were searched using the search terms: ("Transforming growth factor" or TGF-β1) and (polymorphism or variant or variation) and ("fracture" or "bone fracture"). Additional studies were identified by a hand search from reference of original studies or review articles on this topic. There was no language restriction.

Inclusion and exclusion criteria

The following inclusion criteria were used: (1) the study should evaluate the association between the *TGF-β1* +869C/T polymorphism and fracture risk; (2) the study should have a

Table 1. Characteristics of the studies included in this meta-analysis

First author/Year	Ethnicity	Gender	Age	No. of subjects	Quality score
Yamada/1998 1	Asian	Female	69	171	9
Yamada/1998 2	Asian	Female	63	116	8
Bertoldo/2000	Caucasian	Female	60	256	9
Dick/2003	Caucasian	Female	75	1334	7
Ziv/2003	Caucasian	Female	70	3345	8
Lau HHL/2004	Asian	Female	65	237	8
Lau EMC/2004 1	Asian	Female	75	207	7
Lau EMC/2004 1	Asian	Male	73	232	7
Horst-Sikorska/2005	Caucasian	Female	67	187	9
Langdahl/2008	Caucasian	Both	70	28924	10
Herlyn/2010	Caucasian	Both	65	163	7
Mori/2010	Asian	Female	73	168	8

case-control or cohort design; (3) sufficient data should have been provided in order to calculate odds ratios (OR) and 95% confidence interval (CI). Studies were excluded if any of the following conditions applied: (1) only abstracts or reviews were available, without sufficient data; (2) animal studies; (3) studies were repeated or publications overlapped.

Data extraction and qualitative assessment

The following data were recorded from each article: first author, years of publication, ethnicity of participants, gender, age, and numbers of subjects. The data were extracted by two of the authors independently. Discrepancies between these two authors were resolved by discussion.

Two reviewers completed the quality assessment independently. The Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality, which scored studies by the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest. We considered a study awarded 0-3, 4-6, or 7-9 as alow-, moderate-, or high-quality study, respectively. Discrepancies were resolved by consensus and discussion.

Statistical analysis

The strength of association between the *TGF-β1* +869C/T polymorphism and fracture risk was assessed by calculating OR with 95% CI. The pooled ORs were performed for allele model since most of the studies reported the results of this genetic model. A statistical test for heterogeneity was performed based on the Qstatistic. The $P>0.10$ of the Q-test indicated a lack of heterogeneity among studies. The summary OR estimate of each study was calculated by the random-effects model (the DerSimonian and Laird method). Stratified analysis was performed by race and gender. Potential publication bias was examined by Egger's test [16]. All statistical tests were performed with the software STATA version 11.0 (Stata Corporation, College station, TX, USA). A P value <0.05 was considered statistically significant.

Results

Study characteristics

Ten association studies relating to the *TGF-β1* +869C/T polymorphism with susceptibility to fracture met the inclusion requirements for the meta-analysis [6-15]. There were 3 studies performed using Asians, 6 studies using Caucasians. A total of 35340 subjects were included in this meta-analysis. All studies were assessed by NOS. The quality scores ranged from 6 to 10, suggesting that the methodological quality was acceptable. **Table 1** lists the main characteristics of studies for meta-analysis.

Results of meta-analysis

The evaluations of the association between *TGF-β1* +869C/T polymorphism and fracture risk are summarized in **Table 2**. *TGF-β1* +869C/T polymorphismwas associated with a significantly increased risk of fracture (OR=1.41; 95%CI, 1.20-1.65; I^2=0%; **Figure 1**). In the subgroup analysis according to gender, women was significantly associated with risk of fracture (OR=1.44; 95% CI, 1.20-1.73; I^2=4%). In the subgroup analysis by race, Asians (OR=1.43; 95% CI, 1.06-1.92; I^2=0%) and Caucasians (OR=1.44; 95% CI, 1.13-1.85; I^2=15%) showed increased fracture risk.

Table 2. Main result and subgroup analyses of this meta-analysis

Characteristics	No. of studies	Test of association			Model	Heterogeneity		
		OR (95% CI)	*Z*	*P* Value		χ^2	*P* Value	I^2 (%)
All studies	12	1.41 (1.20-1.65)	4.14	<0.0001	R	9.93	0.54	0
Asian	6	1.43 (1.06-1.92)	2.37	0.02	R	4.03	0.54	0
Caucasian	6	1.44(1.13-1.85)	2.90	0.004	R	5.87	0.32	15
Female	9	1.44 (1.20-1.73)	3.94	<0.0001	R	8.33	0.40	4

OR, odds ratio; CI, confidence intervals; R, randomeffects model.

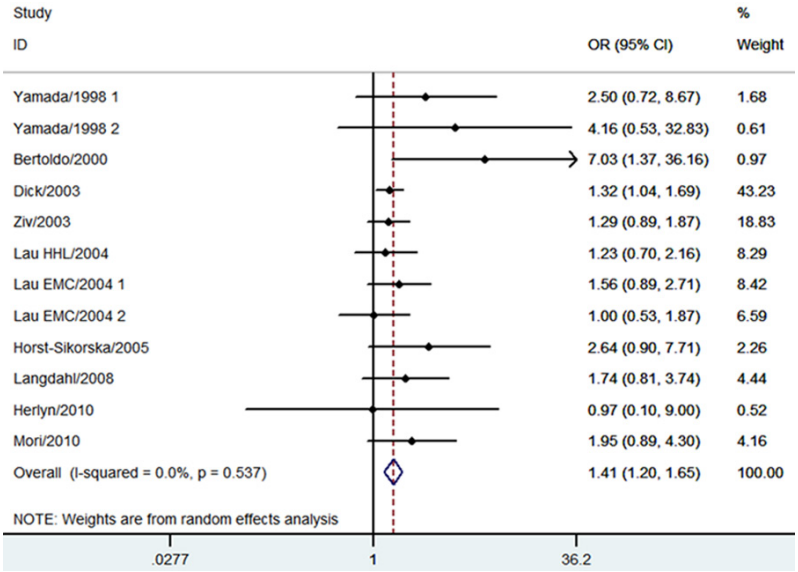

Figure 1. Meta-analysis for the association between *TGF-β1* +869C/T polymorphismand fracturerisk.

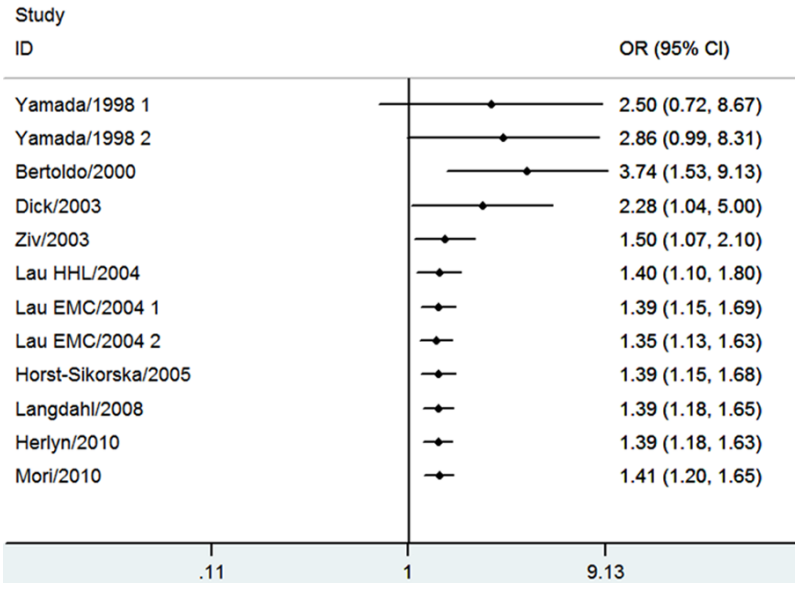

Figure 2. Cumulative meta-analysis for the association between *TGF-β1* +869C/T polymorphismand fracturerisk.

As shown in **Figure 2**, significant associations were evident with each addition of more data over time. The results showed that the pooled ORs tended to be stable. A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs, and the corresponding pooled ORs were not materially altered (**Figure 3**).

Funnel plot was performed to assess the publication bias of literatures. The shape of the funnel plot showed symmetry (**Figure 4**). Egger's test found no evidence of publication bias (*P*=0.115).

Discussion

TGF-β1 has been implicated as a possible mediator of coupling between bone resorption and formation because it can stimulate proliferation or differentiation of preosteoblasts as well as inhibit mature osteoclasts and proliferation of mononuclear osteoclast precursors in vitro [17]. The peptide also inhibits fusion of mononuclear precursors into osteoclast in vitro [18]. TGF-β1 has been implicated as a mediator of the skeletal effects

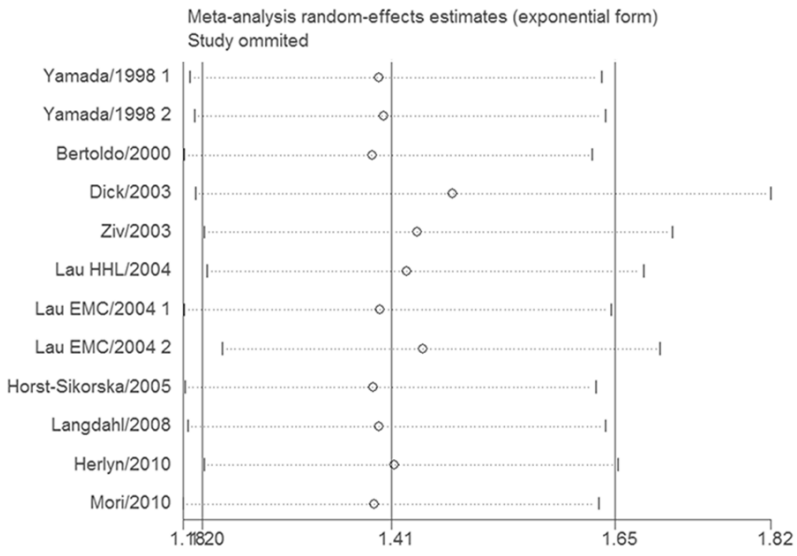

Figure 3. Sensitivity meta-analysis for the association between *TGF-β1* +869C/T polymorphismand fracturerisk.

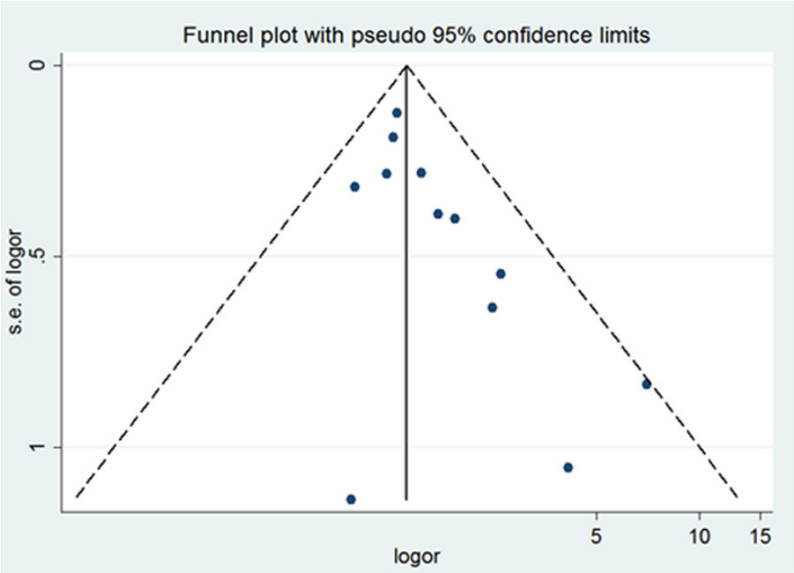

Figure 4. Funnel plot for the association between *TGF-β1* +869C/T polymorphismand fracturerisk.

of estrogen [19]. The production of TGF-β1 by human osteoblasts is stimulated by 17β-estradiol and TGF-β1 contributes to the estrogen-induced boneresorption [20]. Thus, TGF-β1 appeared to play a unique role in the molecular pathogenesis of fracture. *TGF-β1* +869C/T polymorphismhas been identified. Thisallelic variant resulted in significantdifferences with regard to TGF-β1 expression and plasma concentration [21]. Therefore, it is possible that *TGF-β1* +869C/T polymorphism could influence the risk of fracture.

The present meta-analysis including ten studies evaluated the association between *TGF-β1* +869C/T polymorphism and fracture risk. We found that individuals with the *TGF-β1* +869C/T polymorphism showed an increased risk of fracture in the overall population. This result suggested that *TGF-β1* +869C/T polymorphism may be a risk factors of fracture. Population stratification is an area of concern and can lead to spurious evidence for the association between the marker and disease, suggesting a possible role of ethnic differences in genetic backgrounds and the environment they live in [22]. Thus, we carried out stratified analysis by ethnicity. In the stratified analyses by ethnicity, the significant associations were observed in Asians and Caucasians. We also did subgroup analysis in gender. We found that women with *TGF-β1* +869C/T polymorphism showed increased risk of fracture. However, only one study for men was included in this meta-analysis. Thus, the positive association between this polymorphism and fracturecould not be ruled out in men. More studies using men are needed in the future.

Some limitations should be pointed out. First, these results were based on unadjusted estimates that lack the original data from the eligible studies, which limited the evaluation of the effect of the gene-gene interaction during fracture development. Second, we were unable to adjust the meta-analysis to correct for common

fracture risk factors as these were not uniformly reported in the independent investigations.

In conclusion, this meta-analysis found a significant association between *TGF-β1* +869C/T polymorphism and fracture risk. To better understand the potential mechanism for fracture in humans, large well-designed cohort studies are needed to confirm these associations. Further researches should be carried out to explore the effect of genetic networks and environmental factors in different ethnic populations.

Disclosure of conflict of interest

None.

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