Quantitative Assessment of the Association between Polymorphisms in Osteoprotegerin and Bone Mineral Density

Abstract

Background: Low bone mineral density (BMD) predisposes to osteoporosis and elevated risk of fractures. Osteoprotegerin is a soluble molecule associated to metabolism of bone tissue with inhibition of osteoclast-differentiation. Several studies determined the relation among polymorphisms in osteoprotegerin gene and low BMD, but the results are contradictory, so an evaluation about these polymorphisms is necessary. This study carried out a meta-analysis to four polymorphisms in osteoprotegerin gene (A163G, G1181C, T950C, T245G).

Methods: A search in literature was made to identify studies with relevant information. The data was extracted by two investigators independently, following a standardized form. The statistical software Review Manager version 5.2 was used to calculation of heterogeneity ($I^2$), Odds Ratio (OR) and Funnel plots with $P<0.05$.

Results: Nineteen papers with twenty-one eligible studies with 5,120 patients and 4,386 controls were identified. G allele was associated to case group in A163G, G1181C, T950C, T245G polymorphisms (OR = 1.27, 95% CI 1.10, 1.46, $P = 0.0010$; OR = 1.25, 95% CI 1.14, 1.37, $P < 0.00001$; OR = 1.24, 95% CI 1.05, 1.48, $P = 0.01$, respectively). In T950C polymorphism, T allele neither C allele was associated to risk of bone low mineral density. No bias of publication was found in this analysis.
Introduction

Low bone mineral density is a clinical condition present in common diseases such as osteoporosis, and is the single best predictor of osteoporotic fractures and a valuable tool in the evaluation of fracture risk [1].

Studies on twins and on families have shown that as much as 70–80% of the inter-individual variance in bone mineral density at the spine and hip is genetically determined. The genetic contribution to bone mass was observed even into old age, indicating that genes regulate both peak bone mass as well as the rate of bone loss [2].

Several genes have been evaluated to assess their involvement in low BMD [3,4,5] and the osteoprotegerin (OPG) gene is one of the most important candidate genes for osteoporosis, suggested to be associated with low BMD and risk of fractures [6].

Osteoprotegerin is an endogenous receptor antagonist of receptor activator of nuclear factor-κB ligant (RANKL) that is a cytokine responsible for osteoclast differentiation [7]. OPG consequently blocks the effects of RANKL.

The recent studies focus in four polymorphisms in OPG gene: A163G, G1181C, T245G and T950C. These variations already were associated to low Bone Mineral Density [8] and osteoporosis [9]. However the results from others studies [10,11] are contradictories and a better approach forward the association of these polymorphisms is required.

Thus, the aim of this study was to evaluate the influence of the aforementioned polymorphisms and the real risk of low BMD by means of a meta-analysis.

Methods

Strategy of search

A systematic search in literature was performed by three investigators in the electronic biomedical and education databases (Cochrane Library, Google Scholar, MEDLINE and PubMed) to studies published before March 11, 2015 and addressing the association of A163G, G1181C, T245G and T950C polymorphisms in OPG gene and Low Bone Mineral Density. The following combined keywords were used to retrieve the literature: (“osteoprotegerin” or “OPG”) and (“polymorphism” or “SNP” or “A163G” or “G1181C” or “T245G” or “T950C”) and (“low bone mineral density” or “bone mineral density”). No language restriction was placed on the search and all citations of studies were screened to identify additional potential studies.

Inclusion criteria

Articles were included in current meta-analysis if the studies met all the following criteria: (1) Eva-
evaluation of the polymorphisms cited and risk of low bone mineral density; (2) Studies are case/control design; (3) Genotype frequency documented; (4) Diagnosis of low bone mineral density confirmed through radiographic findings and clinical evaluation; (5) The distributions of alleles in study meet in Hardy-Weinberg Equilibrium (HWE). Studies which did not bring sufficient information about genotype or allelic frequencies or did not respect any point these criteria were excluded.

Data extraction
Two investigators (FR and AP) independently reviewed all studies and extracted the data using a standardized form. Data were collected on the authors, year of publication, study design (case, control), number of cases and controls, the polymorphism or polymorphisms evaluated, genotyping method and subject type in study.

Statistical analysis
The statistical analysis of data was performed with use of Review Manager version 5.2 software (RevMan, Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

The chi-squared based Q statistic test ($I^2$) was used to assess the presence of heterogeneity. When heterogeneity was not significant ($I^2 < 50\%, P > 0.05$) the Fixed-effects model was used to estimate the pooled Odds Ratio (OR), when heterogeneity was significant ($I^2 > 50\%, P < 0.05$) and the studies that case this value could not excluded, the Random-effects model was used. Both methods the $P$ value $< 0.05$ was considered statistically significant. Funnel plots (with $P < 0.05$) were used to examine heterogeneity and the publications bias of reported associations and all of data in studies were dichotomous data expressed as OR with 95% of confidence intervals (CI) to assess the association between polymorphisms in OPG gene and low bone mineral density.

Results

Characteristics of eligible studies
Nineteen papers with twenty-one eligible case-control [3,12-29] studies were identified at finish of search in literature as informed in figure 1. In ove-
rall, 5,120 cases and 4,386 controls were included in this meta-analysis. All studies involved women and five from twenty-one studies involved men and women. The basic characteristics of studies were brought in table 1 and all of the genotype and allelic frequencies in case and control groups followed HWE (data no shown).

**Association between A163G polymorphism and risk of low bone mineral density**

Ten studies evaluated the A163G polymorphism in patients with low BMD but one study was excluded because its data carried out elevated heterogeneity in allele evaluations [18]. The meta-analysis of nine studies showed G allele was associated to case group (OR = 1.27, 95% CI 1.10, 1.46, P = 0.0010) (Figure 2-A). The evaluation of genotype combinations was carried out and evidenced elevated association between GG genotype and patients case (Table 2).

**Association between G1181 polymorphism and risk of low bone mineral density**

The meta-analysis of alleles from eleven studies in which one study [14] was excluded because ele-
<table>
<thead>
<tr>
<th>FIRST AUTHOR</th>
<th>STUDY DESIGN</th>
<th>SIMPLE SIZE</th>
<th>AGE (YEARS)</th>
<th>DETECTION METHOD</th>
<th>MUTATION SITE</th>
<th>SUBJECT TYPE</th>
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</thead>
<tbody>
<tr>
<td>BONFÁ et al., 2015</td>
<td>CASE/CONTROL</td>
<td>221/154</td>
<td>33.3 ± 7.3/32.1 ± 7.2</td>
<td>TaqMan</td>
<td>A163G - G1181C - T245G</td>
<td>WOMEN</td>
</tr>
<tr>
<td>BORONOVA et al., 2014</td>
<td>CASE/CONTROL</td>
<td>200/200</td>
<td>DATA NO SHOWN</td>
<td>TaqMan</td>
<td>T245G</td>
<td>WOMEN</td>
</tr>
<tr>
<td>BORONOVA et al., 2014</td>
<td>CASE/CONTROL</td>
<td>180/180</td>
<td>DATA NO SHOWN</td>
<td>TaqMan</td>
<td>A163G - G1181C</td>
<td>WOMEN</td>
</tr>
<tr>
<td>BORONOVA et al., 2015</td>
<td>CASE/CONTROL</td>
<td>48/279</td>
<td>66.92 ± 9.63/64.69 ± 9.18</td>
<td>TaqMan</td>
<td>A163G - G1181C - T245G</td>
<td>WOMEN</td>
</tr>
<tr>
<td>BRADSTROM et al., 2004</td>
<td>CASE/CONTROL</td>
<td>361/497</td>
<td>DATA NO SHOWN</td>
<td>TaqMan</td>
<td>T950C</td>
<td>WOMEN</td>
</tr>
<tr>
<td>BRAMBILA-TAPIA et al., 2012</td>
<td>CASE/CONTROL</td>
<td>41/30</td>
<td>49.3 ± 4.61/48.5 ± 6.13</td>
<td>PCR-RFLP</td>
<td>A163G</td>
<td>WOMEN</td>
</tr>
<tr>
<td>BRANDSTROM et al., 2004</td>
<td>CASE/CONTROL</td>
<td>295/497</td>
<td>75.2 ± 0.16/75.2 ± 0.16</td>
<td>TaqMan</td>
<td>T950C</td>
<td>WOMEN</td>
</tr>
<tr>
<td>DINCEL et al., 2008</td>
<td>CASE/CONTROL</td>
<td>19/21</td>
<td>74.47 ± 8.91/75.47 ± 7.44</td>
<td>HIBRIDIZACION</td>
<td>A163G - T245G</td>
<td>WOMEN</td>
</tr>
<tr>
<td>HSU et al., 2006</td>
<td>CASE/CONTROL</td>
<td>285/290</td>
<td>47.8 ± 7.1/47.7 ± 7.2</td>
<td>TaqMan</td>
<td>A163G - G1181C</td>
<td>WOMEN</td>
</tr>
<tr>
<td>HUSSIEN et al., 2013</td>
<td>CASE/CONTROL</td>
<td>150/50</td>
<td>57.3 ± 3.9/57.3 ± 3.9</td>
<td>PCR-RFLP</td>
<td>A163G</td>
<td>WOMEN</td>
</tr>
<tr>
<td>JORGENSEN et al., 2004</td>
<td>CASE/CONTROL</td>
<td>66/206</td>
<td>68/67</td>
<td>TaqMan</td>
<td>A163G</td>
<td>WOMEN</td>
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<td>KIM et al., 2007</td>
<td>CASE/CONTROL</td>
<td>222/163</td>
<td>57.2 ± 58.0</td>
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<td>WOMEN</td>
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<td>LUNDAHL et al., 2002</td>
<td>CASE/CONTROL</td>
<td>268/327</td>
<td>30-82/20-82</td>
<td>TaqMan</td>
<td>A163G - G1181C - T245G - T950C</td>
<td>WOMEN</td>
</tr>
<tr>
<td>MENCEJ-BEDRAC et al., 2011</td>
<td>CASE/CONTROL</td>
<td>235/243</td>
<td>61.5 ± 8.3/64.4 ± 8.2</td>
<td>PCR-RFLP</td>
<td>G1181C - T245G</td>
<td>WOMEN</td>
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<tr>
<td>MENCEJ-BEDRAC et al., 2009</td>
<td>CASE/CONTROL</td>
<td>239/228</td>
<td>64.5 ± 8.2/61.5 ± 8.3</td>
<td>TaqMan</td>
<td>G1181C</td>
<td>WOMEN</td>
</tr>
<tr>
<td>PIEDRA et al., 2011</td>
<td>CASE/CONTROL</td>
<td>298/114</td>
<td>59 ± 13/62 ± 13</td>
<td>TaqMan</td>
<td>A163G - G1181C - T245G</td>
<td>WOMEN</td>
</tr>
<tr>
<td>VIDAL et al., 2006</td>
<td>CASE/CONTROL</td>
<td>71/52</td>
<td>DATA NO SHOWN</td>
<td>TaqMan</td>
<td>G1181C - T950C</td>
<td>WOMEN</td>
</tr>
<tr>
<td>YAMADA et al., 2003</td>
<td>CASE/CONTROL</td>
<td>1634/555</td>
<td>46.2 ± 0.4/46.3 ± 0.2</td>
<td>FLUORESCENCE</td>
<td>T245G - T950C</td>
<td>WOMEN</td>
</tr>
<tr>
<td>ZAVALE-CERNA et al., 2014</td>
<td>CASE/CONTROL</td>
<td>46/23</td>
<td>49.9/49.9</td>
<td>PCR-RFLP</td>
<td>T245G - T950C</td>
<td>WOMEN</td>
</tr>
<tr>
<td>ZHAO et al., 2005</td>
<td>CASE/CONTROL</td>
<td>134/71</td>
<td>63.0 ± 0.53/61.4 ± 0.71</td>
<td>DIRECT SEQUENCING</td>
<td>G1181C</td>
<td>WOMEN</td>
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</table>

**Table 1.** Characteristic of studies selected to this meta-analysis.
Table 2. Meta-analysis of association between polymorphisms in OPG gene and risk of Low Bone Mineral Density (allelic and genotypic comparisons).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Comparisons (n)</th>
<th>Case/Control (n)</th>
<th>m versus M</th>
<th>M versus m</th>
<th>mm versus Mm/mm</th>
<th>MM versus Mm/mm</th>
<th>mm versus MM</th>
<th>mm versus Mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>A163G</td>
<td>Overall</td>
<td>11</td>
<td>2307/2336</td>
<td>1.25 (1.14, 1.37)</td>
<td>&lt;0.00001</td>
<td>0.80 (0.73, 0.88)</td>
<td>&lt;0.00001</td>
<td>1.19 (1.04, 1.36)</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>1</td>
<td>211/154</td>
<td>1.06 (0.78, 1.43)</td>
<td>0.72</td>
<td>0.95 (0.70, 1.28)</td>
<td>0.72</td>
<td>0.94 (0.61, 1.44)</td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>8</td>
<td>1589/1729</td>
<td>1.12 (1.01, 1.23)</td>
<td>0.04</td>
<td>0.90 (0.81, 0.99)</td>
<td>0.04</td>
<td>1.10 (0.93, 1.30)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>3</td>
<td>507/453</td>
<td>1.36 (1.13, 1.65)</td>
<td>0.001</td>
<td>0.73 (0.61, 0.89)</td>
<td>0.001</td>
<td>1.38 (1.09, 1.74)</td>
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<tr>
<td>G1181C</td>
<td>Overall</td>
<td>11</td>
<td>2307/2336</td>
<td>1.25 (1.14, 1.37)</td>
<td>&lt;0.00001</td>
<td>0.80 (0.73, 0.88)</td>
<td>&lt;0.00001</td>
<td>1.19 (1.04, 1.36)</td>
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<tr>
<td></td>
<td>Mixed</td>
<td>1</td>
<td>211/154</td>
<td>1.06 (0.78, 1.43)</td>
<td>0.72</td>
<td>0.95 (0.70, 1.28)</td>
<td>0.72</td>
<td>0.94 (0.61, 1.44)</td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>8</td>
<td>1589/1729</td>
<td>1.12 (1.01, 1.23)</td>
<td>0.04</td>
<td>0.90 (0.81, 0.99)</td>
<td>0.04</td>
<td>1.10 (0.93, 1.30)</td>
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<tr>
<td></td>
<td>Asian</td>
<td>3</td>
<td>507/453</td>
<td>1.36 (1.13, 1.65)</td>
<td>0.001</td>
<td>0.73 (0.61, 0.89)</td>
<td>0.001</td>
<td>1.38 (1.09, 1.74)</td>
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<tr>
<td>T245G</td>
<td>Overall</td>
<td>9</td>
<td>2404/1996</td>
<td>0.80 (0.68, 0.95)</td>
<td>0.01</td>
<td>1.24 (1.05, 1.48)</td>
<td>0.01</td>
<td>0.08 (0.67, 0.96)</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>2</td>
<td>288/206</td>
<td>1.17 (0.78, 1.76)</td>
<td>0.44</td>
<td>0.85 (0.57, 1.28)</td>
<td>0.44</td>
<td>1.19 (0.76, 1.84)</td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>5</td>
<td>1106/1351</td>
<td>0.78 (0.58, 1.06)</td>
<td>0.11</td>
<td>1.28 (0.94, 1.72)</td>
<td>0.11</td>
<td>0.78 (0.57, 1.08)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>2</td>
<td>1040/439</td>
<td>0.78 (0.60, 1.02)</td>
<td>0.07</td>
<td>1.28 (0.98, 1.68)</td>
<td>0.07</td>
<td>0.78 (0.58, 1.04)</td>
</tr>
<tr>
<td>T950C</td>
<td>Overall</td>
<td>5</td>
<td>1086/1772</td>
<td>1.44 (0.97, 2.14)</td>
<td>0.07</td>
<td>0.72 (0.51, 1.02)</td>
<td>0.07</td>
<td>1.61 (0.93, 2.79)</td>
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<tr>
<td></td>
<td>Mixed</td>
<td>1</td>
<td>65/51</td>
<td>2.00 (1.18, 3.39)</td>
<td>0.01</td>
<td>0.50 (0.30, 0.85)</td>
<td>0.01</td>
<td>3.35 (1.48, 8.44)</td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>3</td>
<td>742/905</td>
<td>1.04 (0.89, 1.22)</td>
<td>0.60</td>
<td>0.96 (0.82, 1.12)</td>
<td>0.60</td>
<td>0.97 (0.75, 1.24)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>1</td>
<td>279/816</td>
<td>0.99 (0.82, 1.21)</td>
<td>0.94</td>
<td>1.01 (0.83, 1.23)</td>
<td>0.94</td>
<td>1.00 (0.76, 1.33)</td>
</tr>
</tbody>
</table>

OR = Odds Ratio, m = wild type allele, M = mutant allele, Mixed = American and Others ethnicities.
vated heterogeneity, G allele and risk of low bone mineral density in this polymorphism evidenced association with case group (OR = 1.25, 95% CI 1.14, 1.37, \( P < 0.00001 \)) (Figure 2-B). In other hand, C allele was associated to control group (OR = 0.80, 95% CI 0.73, 0.88, \( P < 0.00001 \)) in ten studies as well as in evaluation of G allele. Table 2 brings the combinations between genotypes in G1181 polymorphism.

**Association between T950C polymorphism and risk of low bone mineral density**

To evaluate the association between T and C alleles in this polymorphism the Random-effect statistical model was used because only five studies evaluating the T950C polymorphism and low bone mineral density were identified, these total two studies [26,28] carried out elevated heterogeneity. If they had been excluded a few number of studies (three) could invalidate the meta-analysis. Therefore, T allele was no significantly associated to case group (OR = 1.44, 95% CI 0.97, 2.14, \( P = 0.07 \)) (Figure 3-A) and C allele also was no significantly associated to control group (OR = 0.72, 95% CI 0.51, 1.02, \( P = 0.07 \)). The table 2 brings the genotype combinations to T950C polymorphism. With this statistical model used is not possible to build funnel plot.

**Figure 3:** (A) Meta-analysis of T allele in T950C polymorphism. (B) Meta-analysis of G allele in T245G polymorphism.
Association between T245G polymorphism and risk of low bone mineral density

Ten studies evaluated the T245G polymorphism and risk of low BMD, nevertheless, in evaluation of alleles two studies [15,18] were excluded because elevated heterogeneity. Thus, eight papers composed the meta-analysis of alleles in which T allele was associated to control group (OR = 0.80, 95% CI 0.68, 0.95, P = 0.01) and G allele was significantly associated to case group (OR = 1.24, 95% CI 1.05, 1.48, P = 0.01) (Figure 3-B). The combinations of genotypes in T245G polymorphism also were analyzed (Table 2).

Sensitivity analysis and Publication bias

To evaluate the individual effect of studies a sensitivity analysis was performed by omitting each study to assess this impact on pooled ORs. No single publication changed the pooled ORs qualitatively, which suggested that results of this meta-analysis were accurate. The Funnel plots available by statistical software did not reveal any indication of publication bias as showed in figures 4-A, B, and C.

Discussion

OPG is an important mediator of bone remodeling by neutralizing the effects of RANKL with inhibition of osteoclast-differentiation [30]. Several candidate genes for different calciotropic factors known to regulate bone remodeling and variations in these genes can cause changes in bone physiology [11] and a genome-wide study cited the association between polymorphisms in Osteoprotegerin gene and clinical conditions such as osteoporosis [31].

The A163G polymorphism in OPG gene is a mutation occurred in the 5’ flanking region related to risk of fractures and associated to strong linkage disequilibrium with other single nucleotide polymorphisms sites [22]. In this meta-analysis the G allele was associated to patients case group evidenced its role in risk of low bone mineral density. This result contradicts the Choi et al. [32] findings in which A163G polymorphism was not significantly associated to variations in Bone Mass Density.

The A allele was associated to control group (OR = 0.77, 95% CI 0.67, 0.89, P = 0.0003), the results found in meta-analysis of this polymorphism is according with Jørgensen et al. [20]. However the study carried out by Takács et al. [33] showed this polymorphism was not in linkage disequilibrium with rs1564858 SNP, and in this study, A allele has been significantly associated to low bone mineral density as well as the AA and AG genotypes.

In other hand, Langdhal et al. [22], in their study, proved the linkage between A163G polymorphism and G1181C polymorphism, this fact may explain why A allele was associated to control group and G allele was associated to patients case group, whether observed that most of studies included in meta-analysis evaluated these two polymorphism in same patients (Table 1).

In evaluation of G1181C polymorphism the results showed elevated association with C allele and control group. This data corroborates evidences in which G1181C polymorphism as well as CC genotype was associated to normal BMD in Korean patients with Adolescent Idiopathic Scoliosis [34]. A previous study demonstrated G allele and GG genotype carried out a bone mineral density 3.7% lower in women than women with CC genotype [35].

The G allele increased risk of low bone mineral density in postmenopausal women when associated to T950C polymorphism and other SNP (rs4876869) as haplotype [36]. This allele and GG genotype were not associated with BMD variations in postmenopausal Mexican-Mestizo women [37] corroborating data presented in this meta-analysis (Table 2). Nevertheless the stratified evaluation in this polymorphism in mixed population showed data from only one study, so this result must be considered with caution.

The T950C polymorphism was not associated...
Figure 4: Funnel plots of comparison G allele versus A allele in A163G polymorphism (A), G allele versus C allele in G1181C polymorphism (B), and G allele versus T allele in T245G polymorphism (C).
to case group neither control group. These contradicting results can be explained by strong linkage disequilibrium observed in this polymorphism with A163G, G1181C and T245G polymorphism as reported in others studies [22]. T950C polymorphism also was not associated to risk of fracture in elderly Australian women [11] but was associated to variations in BMD in premenopausal women [38].

In stratified analysis by ethnicity showed small variation in OR values. Analysis in Asian ethnicity evidenced a few number of studies, it brings insufficient data about this population resulting in undue conclusions about the influence of these polymorphisms in Asian population.

The association between G allele in T245G polymorphism and bone low density also was showed by this meta-analysis. G allele was identified as a factor associated to decreased of bone mineral density in Korean women when in linkage disequilibrium with A163G polymorphism, although this polymorphism or any combination genotype did show associated to variations in serum OPG levels [39].

The meta-analysis presented in these results had some limitations.

First, most of studies addressed the polymorphisms evaluated in women, specifically (Table 1). The menopause is a condition that accelerates osteoclast activation enhancing the risk of osteoporosis and so low bone mineral density [40] and affects the women. The majority of patients are female, the results could the results may be biased to woman-kind. The small numbers of studies evaluating the polymorphism in men was insufficiently to perform a separate analysis based in gender.

Second, the limited data about ethnicity prevents an stratified analysis is made so disregarding factors that lead to better understanding of these polymorphism and low bone mineral density.

Lastly, currently there are many evidences of the relationship between genetic changes and the development of diseases. Two main types of studies are used to assess this relationship: studies to identify chromosomal regions and polymorphisms studies [41], the latter being more efficient for the detection of genetic diseases that contributions into complex binding studies [42].

Another type of study that can be conducted to assess the interaction between polymorphisms and certain disease is the meta-analysis because from a systematic combination of results of individual studies meta-analysis increases the association of detection capability between factors presenting advantage by overcoming the shortcomings of individual research [43]. Despite such advantages, the meta-analysis does not evaluate polymorphism when identified total linkage disequilibrium.

Although this limitations that could represent bias, no bias of publications was showed by funnel plots validating the results.

Conclusion

This meta-analysis evaluated four polymorphisms (A163G, G1181C, T950C, T245G) in 5,120 patients with low bone mineral density and 4,386 controls showed significant association among G alleles in A163G, G1181C and T245G polymorphism, respectively, and increased risk of low bone mineral density, in complement T950C polymorphism was not significantly associated to risk of low BMD.

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Conflict of Interest

The authors declare that they have no conflict of interests.
Rerences


