Abstract. – OBJECTIVE: To investigate the relationship between blood lipid profiles and osteoporosis in postmenopausal women.

MATERIALS AND METHODS: A comprehensive search of the literature related to lipid profiles and postmenopausal osteoporosis was conducted in Wanfang Database, CNKI, PubMed (1950-2015) and EMBASE (1974-2015). Appropriate studies were selected according to pre-defined exclusion criteria, and the levels of high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (TG) and total cholesterol (TC) were compared between osteoporosis and normal density groups. Statistical analysis was performed using RevMan5.3.

RESULTS: Ten published articles were selected for meta-analysis. The results showed that the levels of HDL, LDL, TC were higher in the osteoporosis group than the normal density group, whereas the levels of TG were lower in the osteoporosis group (HDL: MD = 2.63, 95% CI: 0.43 to 4.84, p = 0.02; LDL: MD = 9.67, 95% CI: -0.10 to 19.44, p = 0.0532; TG: MD = -0.42, 95% CI: -17.52 to 16.67, p = 0.96; TC: MD = 14.82, 95% CI: 2.84 to 26.80, p = 0.02). There was no statistical difference in LDL and TG.

CONCLUSIONS: The serum levels of HDL and TC are higher in postmenopausal osteoporosis patients, and may thus be potentially useful indicators to reflect the process of osteoporosis in these women. More research is needed to determine the relationship between LDL, TG and postmenopausal osteoporosis.

Key Words: Lipid profiles, Osteoporosis, Postmenopausal women, Meta-analysis.

Introduction

With the continuous progress of aging, osteoporosis has become an urgent problem. The results of the 1988-1994 National Health and Nutrition Examination Survey1 showed that osteoporosis substantially decreased the quality of life in people over the age of 50. With the aging of the population, the incidence of osteoporosis continues to rise, bringing huge economic burden to society and families2,3. The susceptibility of fracture was increased in postmenopausal women with osteoporosis4 and fractures involved high morbidity in population with postmenopausal osteoporosis (PMOP)5.

A positive association between cardiovascular diseases (CVD) and osteoporosis was supported by epidemiological studies, where cholesterol has been indicated to be a possible link6,7. Tintut et al8 investigated the role of lipids and lipoproteins on bone and a role for atherogenic lipids and lipoproteins in the pathogenesis of bone loss. However, the association remains unclear. Researchers also show that bone mineral density (BMD) in postmenopausal women is quantitatively associated with blood lipid levels9-13. However, the literature on the relationship between lipids and osteoporosis remains inconsistent. For example, Li et al14 showed that HDL was positively correlated with postmenopausal osteoporosis, but LDL, TG and TC were not. Sivas et al15 found a positive correlation between LDL, TC, TG and postmenopausal osteoporosis. Wang et al16 suggested a negative correlation between LDL, TC and postmenopausal osteoporosis, but there was...
no significant correlation between HDL, TG and postmenopausal osteoporosis. Due to the conflicting results and the insufficient statistical power of individual research, a meta-analysis was conducted to elucidate the relationship between serum lipids and osteoporosis susceptibility in postmenopausal women in our study.

**Materials and Methods**

**Search Strategy and Inclusion Criteria**

A thorough search of the medical literature was conducted in Wanfang Database, China National Knowledge Infrastructure (CNKI, 1994-2015), PubMed (1950-2015) and EMBASE (1974-2015), using the key words “lipid profiles,” “osteoporosis,” and “postmenopausal women.” The complete retrieval type was as below: (‘osteoporosis’ OR ‘postmenopausal osteoporosis’) AND (‘lipid profiles’ OR ‘lipids’ OR ‘triglycerides’ OR ‘low-density lipoprotein cholesterol’ OR ‘high-density lipoprotein cholesterol’ OR ‘total cholesterol’). Date of the last search was August 12th, 2015. The studies needed to meet the following criteria: (1) the subjects were human; (2) the studies were either case-control or cohort studies; (3) the studies focused on the relationship between lipid profiles and osteoporosis in postmenopausal women; (4) subjects in each study were divided into different groups according to their lowest T-score using the WHO classification system: T-score ≥ -1 was regarded as a group with normal BMD, and T-score lower than -2.5 as an osteoporotic group. Included studies only implemented X-ray absorptiometry (DEXA) measurements at the lumbar spine. The exclusion criteria were: (1) subjects were not postmenopausal women; (2) publications were duplicated; (3) studies did not contain lipid profile; (4) serious metabolic disease and patients receiving bone active agents, lipid-lowering medication or corticosteroids; (5) the publication was a review article, commentary or case report.

**Assessment of Methodology Quality**

Assessment of the quality of the included studies was performed according to the following 6 items (Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0).

**Data Extraction**

Observational Studies in Epidemiology (MOOSE) guidelines was applied in this meta-analysis; the following items were extracted from all including researches: author, publication date, country of origin, number of subjects with osteoporosis and number of normal density subjects, age, duration of menopause, BMI (kg/m²), and BMD evaluation method. First, we reviewed the titles and/or abstract for papers; then, we reviewed the full-text publications. All characteristics were extracted according to a protocol. Publication were excluded if they did not meet the above criteria, and provided insufficient data, for example studies without containing lipid profile.

**Statistical Analysis**

The Review Manager Software package (version 5.3; the Cochrane collaboration) was used to perform this meta-analysis. For continuous variables, the weighted mean difference (WMD) were measured with the 95% CIs. WMDs were considered statistically significant at the \( p < 0.05 \) level. \( \chi^2 \) and \( I^2 \) tests were adopted to evaluate the statistical heterogeneity among studies and subgroups. Both fixed-effects (FE) model and a random-effects (RE) model were used to obtain summary WMDs. The FE model was employed with the absence of heterogeneity, otherwise the RE model was employed. Egger’s regression method and the Begg-Mazumdar test were used to assess the publication bias using the software Stata 12.0 (Stata Corp LP, College Station, TX, USA). A sensitivity analysis was performed for the HDL, LDL, TC and TG results using Stata 12.0 software.

**Results**

**Study Characteristics**

A total of 526 relevant studies were identified based on a defined search strategy. By screening the title and abstract, 509 studies were excluded for the following reasons: subjects were not post-menopausal women, the study was review or duplicate, or not cohort or case-control study. Of the remaining 17 articles, two studies were excluded because not all patients met the diagnostic criteria for osteoporosis. The last five studies were excluded because no usable data were available. Finally, 10 articles were eligible for systematic review after critical evaluation. The study selection process is summarized with a flow chart in Figure 1. Our meta-analysis involved a total of 3268 participants, including 1016 osteoporosis patients and 2252 healthy women. The main characteristics of the population in the identified studies are summarized in Table I.
Quality of the Included Studies

A summary of methodological domain assessment for each study is detailed in Figure 2. Only five studies clearly show the blindness in evaluating the results. In general, the risk of bias is considered low-level.

Meta-Analysis

Firstly, we compared HDL in patients with osteoporosis to normal controls (Figure 3). There were significant differences in research heterogeneity when all studies were considered ($I^2 = 75\%, p < 0.0001$). The meta-analysis of 10 studies showed a significant increase in HDL levels in the osteoporosis group compared to the normal group (MD = 2.63, 95% CI: 0.43 to 4.84, $p = 0.02$). Secondly, we compared LDL in osteoporosis cases with normal controls (Figure 4). Similarly, when all studies are considered, research heterogeneity is also significantly different. ($I^2 = 95\%, p < 0.00001$). The meta-analysis of 10 studies showed that the level of LDL in the osteoporosis group was higher than in the normal group. However, in the random effects model, the difference was not statistically significant (MD=9.67, 95% CI:

Table I. Characteristics of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Groups</th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>Duration of menopause (years)</th>
<th>BMI (kg/m²)</th>
<th>BMD evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poli et al 20</td>
<td>Italy</td>
<td>Osteoporosis</td>
<td>217</td>
<td>55.8 ± 4.5</td>
<td>7.4 ± 5.2</td>
<td>22.9 ± 2.9</td>
<td>BMD was evaluated at the lumbar spine (L2-L4) by DEXA</td>
</tr>
<tr>
<td>Cai et al 25</td>
<td>China</td>
<td>Osteoporosis</td>
<td>69</td>
<td>63.32 ± 6.54</td>
<td>14.8 ± 6.13</td>
<td>24.02 ± 3.74</td>
<td>BMD was evaluated at the lumbar spine (L1-L4) by DEXA</td>
</tr>
<tr>
<td>Chen et al 23</td>
<td>China</td>
<td>Osteoporosis</td>
<td>30</td>
<td>63.89 ± 6.65</td>
<td>15.59 ± 7.88</td>
<td>24.85 ± 4.79</td>
<td>BMD was evaluated at the lumbar spine (L1-L4) by DEXA</td>
</tr>
<tr>
<td>Cui et al 24</td>
<td>China</td>
<td>Osteoporosis</td>
<td>50</td>
<td>58.02 ± 9.58</td>
<td>13.15 ± 5.64</td>
<td>24.35 ± 4.26</td>
<td>BMD was evaluated at the lumbar spine (L1-L4) by DEXA</td>
</tr>
<tr>
<td>Sivas et al 27</td>
<td>Turkey</td>
<td>Osteoporosis</td>
<td>36</td>
<td>62.8 ± 6.3</td>
<td>17.5 ± 7.4</td>
<td>29.3 ± 4.5</td>
<td>BMD was evaluated at the lumbar spine (L1-L4) by DEXA</td>
</tr>
<tr>
<td>D’Amelio et al 26</td>
<td>Italy</td>
<td>Osteoporosis</td>
<td>101</td>
<td>61.8 ± 6.1</td>
<td>13.1 ± 1.4</td>
<td>23.01 ± 2.2</td>
<td>BMD was evaluated at the lumbar spine (L1-L4) by DEXA</td>
</tr>
<tr>
<td>Pliatsika et al 22</td>
<td>Greece</td>
<td>Osteoporosis</td>
<td>71</td>
<td>60.9 ± 6.8</td>
<td>12.9 ± 1.57</td>
<td>23.73 ± 2.04</td>
<td>BMD was evaluated at the lumbar spine (L1-L4) by DEXA</td>
</tr>
<tr>
<td>Li et al 28</td>
<td>China</td>
<td>Osteoporosis</td>
<td>297</td>
<td>64.2 ± 6.3</td>
<td>15.2 ± 7.4</td>
<td>22.5 ± 2.9</td>
<td>BMD was evaluated at the lumbar spine (L2-L4) by DEXA</td>
</tr>
<tr>
<td>Yoldemir et al 21</td>
<td>Turkey</td>
<td>Osteoporosis</td>
<td>33</td>
<td>51.17 ± 1.4</td>
<td>2.3 ± 0.7</td>
<td>27.2 ± 1.68</td>
<td>BMD was evaluated at the lumbar spine (L1-L4) by DEXA</td>
</tr>
<tr>
<td>Wang et al 29</td>
<td>China</td>
<td>Osteoporosis</td>
<td>112</td>
<td>66.3 ± 10.2</td>
<td>10.7 ± 4.8</td>
<td>23.5 ± 1.3</td>
<td>BMD was evaluated at the lumbar spine by DEXA</td>
</tr>
</tbody>
</table>
Figure 2. Quality assessment of the included studies.

Figure 3. Meta-analysis results of HDL levels in osteoporosis cases compared with normal controls. Abbreviations: CI, confidence interval; SD, standard deviation.

Figure 4. Meta-analysis results of LDL levels in osteoporosis cases compared with normal controls. Abbreviations: CI, confidence interval; SD, standard deviation.
Lipid profiles and postmenopausal osteoporosis

-0.10 to 19.44, \( p = 0.0532 \). Thirdly, we compared TG in osteoporosis people with normal controls (Figure 5). Also, a significant difference between study heterogeneity was found \( (I^2 = 94\%, p < 0.0001) \), but the TG level was lower than that of the normal group. However, the difference was not statistically significant under a random effect model \( (MD = -0.42, 95\% CI: -17.52 \text{ to } 16.67, p = 0.96) \). Finally, we compared TC in patients with osteoporosis to normal controls (Figure 6). All studies considered significant differences in research heterogeneity \( (I^2 = 95\%, p < 0.0001) \). The meta-analysis of 10 studies showed that TC levels in postmenopausal women with osteoporosis were statistically significant higher than those in the normal group. \( (MD = 14.82, 95\% CI: 2.84 \text{ to } 26.80, p = 0.02) \).

**Sensitivity Analysis and Publication Bias**

The sensitivity analysis showed that the results were not disproportionately influenced by any individual study (Figures 7-10). The Egger's test, conducted using the same software, revealed the funnel pattern's symmetry, indicating no evidence of publication bias \( (p = 0.180 \text{ for HDL}, p = 0.230 \text{ for LDL}, p = 0.087 \text{ for TC}, p = 0.626 \text{ for TG}) \).

**Discussion**

We aimed to investigate whether levels of blood lipid profiles were related to osteoporosis in postmenopausal women. This current research suggested that osteoporosis group had significantly higher HDL and TC level than the normal density group. Our present study also showed that the level of TG was lower in the osteoporosis group than in the normal density group, but the difference was not statistically significant. In addition, our results showed that osteoporosis group had a higher LDL level compared with the normal density group. Our findings strongly suggest that higher HDL and TC were significantly associated

![Figure 5. Meta-analysis results of TC levels in osteoporosis cases compared with normal controls. Abbreviations: CI, confidence interval; SD, standard deviation.](image)

![Figure 6. Meta-analysis results of TG levels in osteoporosis cases compared with normal controls. Abbreviations: CI, confidence interval; SD, standard deviation.](image)
with increased osteoporosis susceptibility. We showed that osteoporosis group had a significant higher HDL level compared to the normal density group. Our reports were consistent with previous findings, which observed a positive correlation between serum HDL level and osteoporosis susceptibility. Otherwise, Poli et al and Cai et al showed no significant association between serum HDL level and osteoporosis susceptibility.

Elevated levels of LDL in the blood can lead to deposits on the cardio-cerebral vascular areas such as the arterial wall. These gradually form atherosclerotic plaques and can block blood vessels. However, literature on the relationship between LDL levels and osteoporosis remains inconsistent. This controversial link between them could be explained partly by a lack of power of individual research. Our meta-analysis showed that osteoporosis group had a higher LDL level compared with the normal density group. Sivas et al, in accordance with our results, observed that LDL-C were associated with BMD. Also, Makovey et al stated a modest inverse relationship between lumbar spine and the whole body BMD and serum LDL levels in post-menopausal women. Additionally, Wang et al and Cui et al have shown a negative relationship between them. Otherwise, Li et al found that LDL levels were not associated with the risk of osteoporosis.

Total cholesterol (TC) refers to the sum of all lipoprotein cholesterol in the blood. High TC can lead to many diseases such as coronary heart disease, diabetes mellitus, cerebral thrombosis and stroke. The menopausal bone loss is mainly caused by the lack of estrogen, a steroid hormone that is an esterified form of cholesterol synthesis. So, the TC levels would be associated with the lower levels of stored estrogen, then affecting the pathogenesis of osteoporosis. Knowing the association between levels of TC and osteoporosis risk in postmenopausal women was very important. Our study found that osteo-
porosis group had significantly higher TC level compared with the normal density group in postmenopausal women. Also, Sivas et al.\textsuperscript{15} found a positive relationship between them. However, Li et al.\textsuperscript{16} observed no correlation between TC level and osteoporosis susceptibility in postmenopausal women. Cui et al.\textsuperscript{23} found a negative relationship between LDL level and risk of osteoporosis. Additionally, previous studies\textsuperscript{27} have shown a modest inverse relationship between lumbar spine and serum TC levels in post-menopausal women. Triglyceride (TG) is the most abundant lipid in the human body. Most organs are able to use triglyceride decomposition products to obtain energy. Also, the liver and other organs can undertake the synthesis of triglycerides, stored in fat tissue. In order to clarify the relationship between TG levels and osteoporosis risk in postmenopausal women, our present study showed no correlation between TG levels and osteoporosis susceptibility. Our findings were similar with previous studies\textsuperscript{11,14-16,24}. Otherwise, Sivas et al.\textsuperscript{15} found a positive relationship between them. Our research has some unique strengths. This may be the first meta-analysis to illuminate the relationship between lipid profiles and postmenopausal osteoporosis. Furthermore, we strictly followed the requirements of meta-analysis and set standard criteria: subjects with effects of lipid or bone altering treatment or serious metabolic disease, were excluded. In addition, all the studies included the provision of lumbar osteoporosis diagnosis. Furthermore, BMD was measured by DEXA, thus increasing the credibility of the outcomes. So far, several factors are regarded to affect bone metabolism and increase the risk of bone fracture. BMI has been positively linked to BMD, as weight poses a mechanical load on bone, leading to stimulation of bone formation. Obesity also induces hormone-mediated mechanisms, mainly due to insulin resistance and hyperinsulinemia. At the same time, they promote bone turnover by stimulating osteoblast activity and inhibiting bone resorption due to adipocyte-associated hormone levels (leptin, estrogen and adiponectin) and other nutrition-related growth factors, rather than by bone-loading effects\textsuperscript{28}. Differences in nutritional patterns (insufficient intake of calcium in low-fat diets and hyperlipidemic patients) may also affect bone density. Some studies explain that interweaving bone mass and blood lipids induce lipid oxidation to promote atherosclerosis formation and to divert stromal marrow cells into adipogenesis rather than osteogenesis. As well as it enhances osteoclastic and impairs osteoblastic activity, thereby reducing bone formation and increasing bone resorption\textsuperscript{29}. The mevalonate pathway may be the link between lipid profile and bone metabolism, explaining the common effects of statins and bisphosphonate treatment on high lipid profile and osteoclastic apoptosis\textsuperscript{28,30}. The exact causality linking these lipid changes to osteoporosis remains to be determined through further studies in this field. Though we applied a DEXA, a golden standard of BMD measurement and a good searching strategy, our study has several limitations. Firstly, lipid profile could observe seasonal variations; however, no subject is stated in the original essay. Secondly, bone mineral density is not only genetically related but also environmental, such as diet and smoking. Our research could not be stratified by factors mentioned above, since primary studies did not provide these data. Lastly, heterogeneity among all the included studies weakened our results to some extent. For these ten publications, five came from China\textsuperscript{14,16,23-25}, two from Turkey\textsuperscript{15,21}, two from Italy\textsuperscript{20,26}, and one from Greece\textsuperscript{22}. Hence, the origin of a population may be a source of heterogeneity. Moreover, age, race and detection methods for different participants also contributed to the heterogeneity. Given this, we performed all meta-analysis using random effects models instead of the fixed-effect model due to high heterogeneity in this work. Therefore, for these reasons, our findings must be taken with caution at the present time.

Conclusions

We provided strong evidence that HDL and TC, but not LDL and TG, were associated with osteoporosis susceptibility in postmenopausal women. The link between them needs to be elucidated in future studies. Though defects in lipids metabolism may be genetic, it is involved with nutritional origin. Anyway, our meta-analysis will help clinicians to screen for osteoporosis and lipid changes to osteoporosis, showing a benefit for osteoporosis in postmenopausal women.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 81472989, to Hong-Xiu Zhang) and the Priority Academic Program Development of Jiangsu Higher Education Institutions.
Conflict of Interest
The Authors declare that they have no conflict of interests.

References


9) OROCCO P. Atherogenic lipid profile and elevated lipoprotein (a) are associated with lower bone mineral density in early postmenopausal overweight women. Eur J Epidemiol 2004; 19: 1105-1112.


25) CAI YB. The research on relationship between the serum lipids, osteoprotegerin and bone mineral density in postmenopausal women. Shanxi Medical University 2010; 1-27.


