Association Between Lipid Biomarkers and Osteoporosis: A Cross-Sectional Study

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Research article

Keywords: lipid biomarkers, osteoporosis, bone mineral density (BMD), risk assessment

Posted Date: October 28th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-97252/v1>

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Abstract

Background: Osteoporosis and cardiovascular diseases (CVDs) are two major public health problems. Osteoporosis and CVDs may be linked but the association between lipid profile and osteoporosis is still controversial. The purpose of this study was to examine the associations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) with osteoporosis.

Methods: Using inpatients' electronic medical records (EMR) and dual X-ray absorptiometry (DXA) database stored at The Second Hospital of Jilin University, we included 481 patients with complete and valid lipid and bone mineral density (BMD) data in 2017. Serum samples were used to measure TC, LDL-C, HDL-C and TG. Femoral neck and total hip BMD were measured by DXA; osteoporosis was defined as femoral neck or total hip T-score ≤ -2.5 . Multivariable logistic regression models were used to test the associations of TC, LDL-C, HDL-C and TG with osteoporosis.

Results: The mean age for included patients was 62.7 years (SD = 8.6 years); 60.1 % of them were female. Each standard deviation (SD) increase in TC (Odds Ratio [OR]: 1.43; 95% Confidence Interval [CI]: 1.03-1.99) and TG (OR: 1.60; 95% CI: 1.12-2.30) were associated with increased risk of osteoporosis; LDL-C and HDL-C levels were not associated with osteoporosis. Age, sex and body mass index (BMI) did not interact the relationships of TC and TG with osteoporosis (all $P > 0.10$).

Conclusions: Higher TC and TG levels were associated with greater risk of osteoporosis.

1. Introduction

Worldwide, osteoporosis and cardiovascular diseases (CVDs) are two major public health problems [1, 2]. Up to 49 million individuals have osteoporosis in North America, Europe, Japan, and Australia [3]. In 2017, CVDs lead to approximately 17.8 million deaths worldwide [4, 5]. Osteoporosis and CVDs both significantly increase risk of morbidity and mortality [6, 7].

Osteoporosis and CVDs may be linked [8, 9]. Osteoporosis and CVDs share many risk factors, such as advancing age, premature menopause, genetics, a sedentary lifestyle and smoking, etc. [10, 11]. There is evidence suggesting that individuals with CVDs have 1.69 folds higher risk of osteoporosis than those without CVDs [12]. In addition, osteoporotic patients are 1.2 to 1.4 times more susceptible to cardiovascular events than those without osteoporosis [10, 13].

Lipid profile is useful for assessing risk of CVDs [14]. There is also *vitro* evidence suggesting lipids are involved in the development of osteoporosis [15]. However, the association between lipid profile and osteoporosis in human studies is still controversial [16–25]. Majority of human studies suggested there were negative associations between lipid biomarkers and bone mineral density (BMD) [16, 17, 19, 22–25]. However, Ersoy et al. [18] and Lahon et al. [20] found that low-density lipoprotein cholesterol (LDL-C) was positively correlated with BMD. Ghadiri-Anari et al. [21] suggested a null association between lipids and

BMD. The purpose of this study was to examine the associations of total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) with osteoporosis.

2. Methods

2.1 Study setting and subjects

The data was drawn from inpatients' electronic medical records (EMR) and dual X-ray absorptiometry (DXA) database stored at The Second Hospital of Jilin University, which is located in the northeast part of China. The Second Hospital of Jilin University has 62 clinical departments (i.e., endocrinology, bone and cardiology) and 8 medical technology departments (i.e., clinical laboratory and nuclear medicine). The hospital has more than 2,789 beds, 4,000 faculty members and staffs; its annual outpatients and inpatients are approximately 1.81 million and 0.11 million, respectively. The Second Hospital of Jilin University is a major diagnosis and treatment center for severe diseases (i.e., cancers and CVDs) for the whole Jilin Province in China. The linked for EMR and DXA databases capture patients demographics (i.e., age and sex), anthropometry data (e.g., body height and weight), clinical laboratory measurement records, prescription drug dispensation records, clinical diagnoses and BMD data.

We identified patients with complete and valid data on femoral neck and total hip BMD, TC, LDL-C, HDL-C and TG in 2017 in this study. We excluded patients: (1) with age < 50 years old at BMD test; (2) with early (< 40 years) menopause; (3) with a lipid-lowering therapy, synthroid or hormone-replacement therapy; (4) with osteoporosis-related diseases such as cancer, thyroid disease, hypopituitarism, rheumatoid arthritis, chronic renal failure or renal dysfunction (creatinine > 442 $\mu\text{mol/L}$), chronic liver disease or liver dysfunction (aspartate aminotransferase or alanine aminotransferase > 80 U/L); (5) with a surgical history of bilateral salpingo-oophorectomy menopause or a history of bone surgery at the lumbar spine or hip. To partially exclude patients with osteoporosis-related medications, we only included the patients at their first DXA tests. This study was approved by The Second Hospital of Jilin University Life Science Ethics Committee (2017 Research Approval No.13).

2.2 BMD measurement

Femoral neck and total hip BMD were measured by a DXA fan-beam bone densitometer (Discovery Wi, Hologic, Bedford, MA, USA). The control spine phantom scan performed each day had a long-term (more than 5 years) coefficient of variation (CV) of < 0.5%. We defined osteoporosis as femoral neck or total hip T-score ≤ -2.5 [26]; the reference for calculating T-score was based on BMD data from Whites 20–29 years old in the third National Health and Nutrition Examination Survey (NHANES III) [27].

2.3 Blood draw and storage

Fasting blood samples (≥ 8 hours) were drawn from patients with spray-coated silica and a polymer gel evacuated sterile collection tubes (BD, Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA) by nurses; these blood samples were centrifuged to obtain serum at clinical laboratory department.

2.4 Lipid biomarkers ascertainment

Within two hours following blood draw, serum samples were used to directly measure TC, LDL-C, HDL-C and TG; their levels were determined by a biochemical analyzer (7600 model, Hitachi, Tokyo, Japan). The CVs for TC, LDL-C, HDL-C and TG measurements were 2.5%, 3.1%, 5.1% and 1.9%, respectively.

2.5 Covariate ascertainment

The covariates were extracted from EMR and DXA databases. The covariates for this study included demographics variables (sex, age), anthropometric variables (height, weight, body mass index [BMI]), disease diagnoses (type 2 diabetes, neuropathy, hypertension, retinopathy, ischemic heart disease, ischemic stroke, diabetic nephropathy and osteoarthritis), medication for diseases (calcium channel blockers, angiotensin 2 receptor blockers, beta-blockers, diuretics, angiotensin converting enzyme inhibitors), liver function biomarkers (alanine transaminase, aspartate aminotransferase, total protein, albumin, total bilirubin, direct bilirubin, gamma-glutamyltransferase), bone biomarkers (alkaline phosphatase, calcium, phosphorus), thyroid function biomarkers (free thyroxine 4, thyroid-stimulating hormone), glycated hemoglobin A1c and fasting glucose. The covariates included in the analysis could be potential confounders that maybe associated with femoral neck or total hip BMD. Alanine transaminase, aspartate aminotransferase, total protein, albumin, total bilirubin, direct bilirubin, gamma-glutamyltransferase, alkaline phosphatase, calcium, phosphorus and fasting glucose were measured with a biochemical analyzer (7600 model, Hitachi, Tokyo, Japan) and free thyroxine 4, thyroid-stimulating hormone with a chemiluminescent microparticle immunoassay analyzer (Architect i2000sr model, Abbott, Chicago, USA) and glycated hemoglobin A1c with an automatic glycosylated hemoglobin analyzer (D-10, Bio-Rad, California, USA).

Height and weight were measured using a wall-mounted stadiometer (to the nearest 0.1 cm) and an electronic scale (to the nearest 0.1 kg) and stored in the DXA database. BMI was calculated as weight (kilograms) divided by the square of the height (meters). Disease diagnoses (including type 2 diabetes, neuropathy, hypertension, retinopathy, ischemic heart disease, ischemic stroke, diabetic nephropathy and osteoarthritis) and medication for diseases (including calcium channel blockers, angiotensin 2 receptor blockers, beta-blockers, diuretics, angiotensin converting enzyme inhibitors) were also extracted from EMR, they were either self-report or clinically diagnosed with specific criteria.

2.6 Statistical analysis

We showed continuous variables as means (standard deviations [SDs]) or medians (inter-quartile ranges), categorical variables as frequencies (percentages). Statistical differences between osteoporotic and non-osteoporotic patients for characteristics of patients were tested with the student *t* test or chi-square test.

Multivariable logistic regression models were used to test the associations of TC (per SD increase), LDL-C (per SD increase), HDL-C (per SD increase) and TG (per SD increase) with osteoporosis. Due to the high correlations between lipid biomarkers (Pearson *r* up to 0.70), we included each lipid biomarker in one model. Models were further adjusted for sex, age, BMI, type 2 diabetes, neuropathy, calcium channel

blockers, angiotensin converting enzyme inhibitors, alanine transaminase, albumin, total bilirubin, gamma-glutamyltransferase and alkaline phosphatase; variables considered but not included in the adjusted model were hypertension, retinopathy, ischemic heart disease, ischemic stroke, diabetic nephropathy, osteoarthritis, angiotensin 2 receptor blockers, beta-blockers, diuretics, aspartate aminotransferase, total protein, calcium, phosphorus, free thyroxine 4, thyroid-stimulating hormone, glycated hemoglobin A1c and fasting glucose, because they failed to meet $P < 0.10$ criteria under univariate analyses with osteoporosis. Because total bilirubin and direct bilirubin are highly associated ($r = 0.80$), to avoid the effect of colinearity, direct bilirubin was not included in the multivariable logistic regression models. There were 1.25%, 1.46%, 1.66%, 1.46% and 1.46% missing data for alanine transaminase, albumin, total bilirubin, gamma-glutamyltransferase and alkaline phosphatase. According to Downer et al.'s methods [28], these missing data were classified into an independent category while we adjusted them in the model.

TC, LDL-C, HDL-C and TG were classified as normal and abnormal groups according to their clinical reference values. Multivariable logistic regression models were used to test the associations of each lipid biomarker group with osteoporosis. Models were adjusted for sex, age, BMI, type 2 diabetes, neuropathy, calcium channel blockers, angiotensin converting enzyme inhibitors, alanine transaminase, albumin, total bilirubin, gamma-glutamyltransferase and alkaline phosphatase.

Multivariable linear regression models were used to test the associations between lipid biomarkers and femoral neck or total hip BMD. Models were adjusted for sex, age, BMI, type 2 diabetes, neuropathy, calcium channel blockers, angiotensin converting enzyme inhibitors, alanine transaminase, albumin, total bilirubin, gamma-glutamyltransferase and alkaline phosphatase. All analyses were conducted with SPSS (version 24.0, IBM, Inc., New York, USA) and two-sided P values < 0.05 were considered statistically significant.

3. Results

After excluding ineligible individuals (Fig. 1), we included 481 patients for this study (Number of females: 289 [60.1%]). As compared to excluded patients, included patients were older (62.7 vs 45.2 years; $P < 0.001$) and more likely to be female (60.1 vs 49.0%; $P < 0.001$); BMI was not significantly different between included and excluded patients (25.7 vs 25.7 kg/m²; $P = 0.886$).

Among included patients, 357 (74.2%), 228 (47.4%) and 84 (17.5%) patients had type 2 diabetes, hypertension and ischemic heart disease diagnoses, respectively. The mean age for included patients was 62.7 years (SD = 8.6 years); 60.1% of participants were female; the average BMI for included participants was 25.7 kg/m² (SD = 3.5 kg/m²). As shown in Table 1, osteoporotic patients tended to be older, more likely to be female and had higher proportion of calcium channel blockers medication, angiotensin converting enzyme inhibitors medication, higher levels of TC, alkaline phosphatase and a lower proportion of type 2 diabetes, lower levels of BMI, alanine transaminase, albumin, total bilirubin, direct bilirubin and gamma-glutamyltransferase.

Table 1
Characteristics of study participants by osteoporosis status

Variable	No Osteoporosis (n = 411)	Osteoporosis (n = 70)	<i>P</i>
Demographics			
Female (n, %)	224 (54.5)	65 (92.9)	< 0.001
Age (years)	61.5 (8.0)	70.1 (8.4)	< 0.001
Anthropometry			
Height (cm)	162.8 (8.6)	153.7 (5.8)	< 0.001
Weight (kg)	68.9 (11.4)	57.1 (9.3)	< 0.001
Body mass index (kg/m ²)	26.0 (3.4)	24.2 (3.8)	< 0.001
Disease diagnoses			
Type 2 diabetes (n, %)	317 (76.39)	40 (60.61)	0.007
Neuropathy (n, %)	199 (48.42)	26 (37.14)	0.081
Hypertension (n, %)	198 (47.71)	30 (45.45)	0.733
Retinopathy (n, %)	104 (25.30)	16 (22.86)	0.662
Ischemic heart disease (n, %)	70 (16.87)	14 (21.21)	0.388
Ischemic stroke (n, %)	10 (2.41)	3 (4.55)	0.320
Diabetic nephropathy (n, %)	7 (1.69)	2 (3.03)	0.454
Osteoarthritis (n, %)	6 (1.45)	1 (1.52)	0.965
Medication for diseases			
Calcium channel blockers (n, %)	34 (8.27)	11 (15.71)	0.048
Angiotensin 2 receptor blockers (n, %)	22 (5.35)	3 (4.29)	0.710
Beta-blockers (n, %)	9 (2.19)	2 (2.86)	0.730
Diuretics (n, %)	6 (1.46)	1 (1.43)	0.984

^aVariables are shown as medians (inter-quartile range). Unless otherwise specified, values are shown as means (standard deviations).

Variable	No Osteoporosis (n = 411)	Osteoporosis (n = 70)	<i>P</i>
Angiotensin converting enzyme inhibitors (n, %)	2 (0.49)	2 (2.86)	0.044
Lipid biomarkers			
Total cholesterol (mmol/L)	5.06 (1.26)	5.42 (1.35)	0.028
Low-density lipoprotein cholesterol (mmol/L)	2.85 (0.86)	3.04 (0.99)	0.101
High-density lipoprotein cholesterol (mmol/L)	1.14 (0.31)	1.19 (0.31)	0.235
Triglyceride (mmol/L) ^a	1.57 (1.12, 2.44)	1.83 (1.27, 3.05)	0.189
Liver function biomarkers			
Alanine transaminase (U/L) ^a	21.00 (15.00, 30.00)	16.50 (11.00, 22.00)	0.008
Aspartate aminotransferase (U/L) ^a	18.00 (15.00, 23.00)	17.00 (15.00, 22.00)	0.420
Total protein (g/L)	71.35 (6.47)	70.32 (8.17)	0.242
Albumin (g/L)	43.10 (4.21)	41.12 (5.32)	< 0.001
Total bilirubin (μmol/L)	13.10 (5.54)	11.51 (5.15)	0.027
Direct bilirubin (μmol/L) ^a	3.25 (2.27, 4.49)	2.60 (1.90, 3.99)	0.092
Gamma-glutamyltransferase (U/L) ^a	27.00 (20.00, 43.00)	20.00 (15.00, 33.00)	0.010
Bone biomarkers			
Alkaline phosphatase (U/L)	89.75 (28.98)	108.20 (51.70)	< 0.001
Calcium (mmol/L)	2.34 (0.13)	2.31 (0.15)	0.170
Phosphorus (mmol/L)	1.13 (0.20)	1.12 (0.21)	0.625
Thyroid function biomarkers			
Free thyroxine 4 (Ft4)(pmol/L)	15.94 (3.15)	16.36 (11.45)	0.575
Thyroid-stimulating hormone (TSH) (mIU/L) ^a	2.03 (1.23, 3.11)	1.98 (0.96, 3.74)	0.881

^aVariables are shown as medians (inter-quartile range). Unless otherwise specified, values are shown as means (standard deviations).

Variable	No Osteoporosis (n = 411)	Osteoporosis (n = 70)	<i>P</i>
Other biomarkers			
Glycated hemoglobin A1c (%)	8.96 (2.10)	8.45 (2.25)	0.112
Fasting glucose (mmol/L)	9.20 (3.76)	8.63 (5.04)	0.301
^a Variables are shown as medians (inter-quartile range). Unless otherwise specified, values are shown as means (standard deviations).			

As shown in Table 2, among all 481 patients, in the adjusted model, each SD increase in TC (Odds Ratio [OR]: 1.43; 95% Confidence Interval [CI]: 1.03–1.99) and TG (OR: 1.60; 95% CI: 1.12–2.30) were associated with increased risk of osteoporosis; LDL-C and HDL-C were not associated with osteoporosis. Age, sex and BMI did not interact the relationships of TC and TG with osteoporosis (all $P > 0.10$). We observed identical associations when BMD was treated as continuous variables (Table S1). After classifying lipid biomarkers according to their clinical cut-off values, we found abnormal higher TG levels in serum were associated with higher risk of osteoporosis (Table S2).

Table 2

ORs*and 95% CIs for osteoporosis associated with lipid biomarkers (per standard deviation increase)

Independent Variable	Unadjusted		Adjusted	
	<i>P</i>	OR (95%CI)	<i>P</i>	OR (95%CI)
Total cholesterol	0.030	1.30 (1.03–1.66)	0.031	1.43 (1.03–1.99)
Low-density Lipoprotein cholesterol	0.102	1.23 (0.96–1.58)	0.108	1.29 (0.95–1.75)
High-density Lipoprotein cholesterol	0.235	1.16 (0.91–1.48)	0.447	1.14 (0.82–1.59)
Triglyceride	0.195	1.18 (0.92–1.50)	0.011	1.60 (1.12–2.30)
*Adjusted for sex, age, body mass index, type 2 diabetes, neuropathy, calcium channel blockers, angiotensin converting enzyme inhibitors, alanine transaminase, albumin, total bilirubin, gamma-glutamyltransferase and alkaline phosphatase.				

4. Discussion

In this study, we demonstrated that in northeast China, among patients aged ≥ 50 years, higher TC and TG levels were associated with greater risk of osteoporosis. Serum LDL-C and HDL-C levels were not associated with osteoporosis.

The positive relationships of TC and TG levels with osteoporosis in our study are consistent with some previous studies [19, 23, 25, 29]. Lahon et al.[20] and Ersoy et al.[18] reported a negative correlation between TC and TG levels and osteoporosis. In addition, Ghadiri-Anari et al.[21], Cui et al.[22], Li et al.[24] and Jeong et al.[30] found that there was no association between lipid profiles and osteoporosis. These results are not in line with our findings. The underlying reasons are still unclear, but they may be related to the differences in study populations and osteoporosis risk factors (i.e., lifestyle).

Regardless of consistent or conflicting findings, the positive associations of TC and TG levels with BMD can be explained by several biological mechanisms. First, the nuclear hormone receptor peroxisome proliferator activated receptor γ (PPAR γ) may play a role in the relationship of lipid biomarkers and BMD. PPAR γ can be activated by lipid metabolites. When PPAR γ level increases, osteogenesis is inhibited [31]; this leads to increased bone loss. Second, higher lipid levels are associated with an increase in oxidized lipids and higher oxidative stress levels. Higher oxidative stress level could inhibit osteoblast differentiation as well as to promote adipocyte differentiation [32, 33]. Third, higher serum TG levels are positively associated with higher bone marrow fat [34], which leads to lower trabecular BMD [35].

Several limitations for this study are acknowledged. First, the findings were derived from a cross-sectional study. Therefore, we cannot make causal inference about the association between lipid biomarkers and BMD. Second, we only analyzed the patients who attended The Second Hospital of Jilin University; there were also differences between included and excluded patients in terms of sex and age. There was potential selection bias for this research. Third, 74.2% of included individuals were type 2 diabetic patients. While the prevalence of type 2 diabetes in Jilin Province is 17.5% [36]. Most of the study patients came from clinical endocrine department, this may lead to higher proportion of type 2 diabetes in our study. Type 2 diabetic patients have comorbidities (i.e., neuropathy and retinopathy) and use anti-diabetic medications (i.e., insulin), these could be potential factors for the development of osteoporosis [37]. Moreover, data on anti-diabetic medications are not available in our study; this may negatively affect the reliability of our results [38]. Fourth, there are no data on osteoporosis medications in our study. Because osteoporosis condition is often undiscerned until under DXA tests, patients may seldom take medications for osteoporosis before DXA tests, thus we only include patients at their first DXA tests in the hospital in our study to partially exclude the patients taking anti-osteoporosis medication. Last, due to the absent data, we did not consider osteoporosis factors such as patients' lifestyle factors and nutrition condition in the study. Some critical life style behaviors such as smoking and drinking habits, physical activity, socioeconomic variables and receiving glucocorticoids were lacking. This may negatively impact the reliability of our results.

In conclusion, there were associations between serum TC and TG and osteoporosis in the studied population. These findings extended our understanding about the lipid profile and BMD, especially among a northeast population in China. High quality prospective studies on relationship between lipid biomarkers and BMD are still warranted to confirm our results.

Abbreviations

CVDs: cardiovascular diseases; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; EMR: electronic medical records; DXA: dual X-ray absorptiometry; BMD: bone mineral density; SD: standard deviation; OR: odds ratio; CI: confidence interval; BMI: body mass index; NHANES III: the third National Health and Nutrition Examination Survey; SDs: standard deviations; PPAR γ : peroxisome proliferator activated receptor γ .

Declarations

Acknowledgements

Not applicable.

Authors' contributions

QQZ: Conceptualization, Data curation, Investigation, Methodology –Writing review & editing.

BK: Writing –Writing original draft, Formal analysis.

LJW: Data curation –Writing review & editing.

SSX: Investigation –Writing review & editing.

HQC: Conceptualization, Methodology, Supervision, Validation –Writing review & editing.

SMY: Conceptualization, Funding acquisition, Methodology, Supervision, Validation –Writing review & editing.

All authors read and approved the final manuscript.

Funding

This work was supported by a grant from the Jilin Provincial Department of Education in China (JJKH20190090KJ).

Availability of data and materials

The availability of data needs ethical approval from The Second Hospital of Jilin University Life Science Ethics Committee.

Ethics approval and consent to participate

This investigation was approved by The Second Hospital of Jilin University Life Science Ethics Committee (Ethic approval code: 2017 Research Approval No.13). The content is solely the responsibility of the authors and does not represent the official views of The Second Hospital of Jilin University. Written informed consent was obtained for all participants.

Consent for publication

Not applicable.

Competing interests

Qianqian Zhao, Bo Kan, Lijuan Wang, Shanshan Xue, Hanqing Cai, and Shuman Yang declare that they have no competing interests.

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Figures

Figure 1

Flow chart for cohort inclusion and exclusions

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