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Serum Lipids Effect on Bone Mineral Density: A Pilot Study in Apparently Healthy Syrians

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Abstract

Objective: Dyslipidemia is suggested to be one of factors that affect bone mineral density (BMD). However, epidemiological studies concerning relationship between serum lipids and BMD showed different results. Absent, positive, or negative relations have been reported.

The aim of this study was to investigate the correlation between serum lipids and BMD in a group of apparently healthy Syrians.

Methods: This pilot cross-sectional study was carried out at one of Damascus University Hospitals. 152 apparently healthy Syrians aged 20-50 years were enrolled.

Serum cholesterol, low density lipoprotein, high density lipoprotein, and triglyceride were measured.

BMD of lumbar spine, femoral neck and total hip were assessed by Dual-energy X-ray Absorptiometry (DXA) using Discovery Wi (S/N80058) scan (Hologic, Inc. Bedford, MA). Pearson correlation test was used to assess the relation between each lipid profile component and BMD of each measured skeletal site.

Results: No statistically significant relationship was found between serum lipids components and BMD at any measured skeletal site. Adjustment for gender, age, smoking, and body mass index did not alter the results (P value for all was >0.05).

Conclusion: Our findings do not support the hypothesis that there is a relationship between serum lipids and BMD.

Keywords: Lipid profile; Bone Mineral Density (BMD); Osteoporosis; Fragility fractures

Introduction

Osteoporosis became a major public health problem, more than 10 million Americans have osteoporosis, and more than 34 million others have low bone mass. This put them at risk of fracturing. Some studies reported that osteoporotic fractures lifetime risk is very high ranging from 40-50% in women and 13-22% in men. Increased morbidity and mortality of fragility fractures caused a heavy economic burden. For instance, the cost of these fractures in the USA in 2005 was approximately $17 billion [1,2]. Bone mineral density (BMD) is the gold standard for diagnosing osteoporosis and fractures risk assessment [3]

There are many well established factors affecting BMD such as: aging, glucocorticoids treatment, smoking, and low physical activity [4]. Dislipidemia was suggested to be one of these factors based on many observations.

On the first hand, it was reported that lipid levels might explain the link between atherosclerosis and osteoporosis [5]. This link was suggested by some epidemiological studies that reported an increased risk for cardiovascular events in osteoporotic postmenopausal women independent of their ages [6,7]. Other studies also found that aortic calcification (a marker for atherosclerosis) is associated with increased risk of osteoporotic fractures [8].

On the second hand, some studies reported that Statin use has been associated with improvement of BMD and reduction in fracture risk [9,10].

Moreover, data from the national health and nutrition examination survey (NHANES III) revealed that 63% of osteoporotic women have hypercholesterolemia (Cholesterol ≥ 200 mg/dl) and 53% have high low density lipoprotein (LDL ≥ 130 mg/dl) [11].

It was shown that under atherogenic lipid profile LDL particles may accumulate in subendothelial matrix of bone vessels [12], where they go under nonenzymatic oxidation by osteoblasts [12,13]. Oxidized lipids were reported to inhibit osteoblasts differentiation [14,15], reduce their viability [13] and increase their apoptosis [16]. They were also found to affect bone resorption by increasing osteoclastogenesis cytokines production such as receptor activator of nuclear factor-κB (RANKL) and interleukin-6 from both T-lymphocytes and osteoblasts [17-21]. Furthermore, it has been reported that oxidized lipids down regulate parathyroid hormone receptor (PTH1R) in osteoblasts causing resistance to PTH [22-26].

However, epidemiological studies concerning relationship between lipid levels and BMD have conflicting results. While some studies showed no effect of dislipidemia on BMD [27-30], others reported that there is either a negative [31-35] or a positive effect [36-38].

While Orozco in 2004 showed that postmenopausal women with atherogenic lipid profiles had lower BMD in lumbar spine and femoral neck [34]; Brownbill et al. in 2006 showed that BMD is higher with higher levels of serum triglyceride and cholesterol [36]. Whereas, Jeong-Ho Go et al. in 2012 found no association between serum lipids and BMD in postmenopausal Korean women [28].

Most studies concerning lipid profile and BMD relationship were carried out in western and Asian populations with few studies in middle east countries such as Iran and Turkey [39,40], this calls for more studies in this area because people there might have different bone mineral densities with different response for dyslipidemia. El-Hajj Fuleihan et al. reported that peak BMD in Lebanese subjects is 0.2-0.9 standard deviation (SD) below peak BMD in American subjects [41].

The aim of this pilot study was to investigate the relationship between BMD and serum lipids in a group of apparently healthy Syrians. The novelty of this study was, as far as we know, because it is the first study concerning this issue in Syria.

Material and Methods

This observational cross-sectional pilot study was approved by Damascus university institutional review board. Informed consent were taken from each participant. It was performed between January 2013 and February 2014 in Al-Assad University Hospital (AUH). AUH is a central, teaching hospital that serves as one of major tertiary referral hospitals for a district (Mohafazat) Damascus. (http://auhd.edu.sy/en).

Recruited subjects were volunteers who responded to the study advertisement for apparently healthy subjects from both genders aged 20-50 years.

Exclusion criteria included pregnant and postmenopausal women, women with menstrual irregularity, subjects with any acute or chronic disease, and subjects on any medications that affect BMD or lipid levels such as hormone replacement therapy (HRT), hormonal contraceptives, Bisphosphonates, Vitamin D, Statins and other lipid lowering agents.

There was no alcohol intake. All participants were either non-smokers (never smoked or had smoked <100 cigarettes in their whole life) or smokers.

Anthropometric measurements were performed by the same person using the same standardized techniques and calibrated digital scale (Seca, Germany). Body mass index (BMI) was calculated for all subjects wearing light clothing and no shoes, as weight in kilograms (kg) divided by squared height in meters (m).

Laboratory measurements

12-hours overnight fasting blood sample was obtained from each participant.

All blood samples were analysed immediately after blood was drawn by the same team of technicians and the same method was used throughout the study period, using kits provided by the same manufacturer.

Total cholesterol (CHOL), low density lipoprotein (LDL), High density lipoprotein (HDL), Triglyceride (TG) , Glucose (Glu), Createnin (Cr), Alkaline phosphatase (ALP), Calcium (Ca), Albumin(Alb), phosphorus (P) and Alanine transaminase (ALT) were measured by standard colorimetric methods using Roche Hitachi 912 autoanalyzer (Roche Diagnostics, Mannheim, Germany).

Thyroid stimulating hormone (TSH) and Free thyroxine (FT4) levels were measured using automated electrochemiluminescence immunoassay (Elecsys 2010 analysers, Roche Diagnostics GmbH, Mannheim

Participants who had any disturbance in these laboratory results (other than lipid profile components) were excluded.

Bone mineral density measurement

BMD was measured by Dual-energy X-ray absorptiometry (DXA) using Discovery Wi (S/N 80058) scan (Hologic, Inc. Bedford, MA). BMD was measured at lumbar spine (L1-L4 and total lumbar), femoral neck and total hip.

All BMD measurements were performed by the same expert technician. Calibration was done using the phantoms provided with the device.

Results were expressed as BMD in gram per square centimetre.

Statistical analysis

Statistical analyses were performed using the Predictive Analytics Software Statistics (PASW Statistics) version 18. Results were expressed as means ± SD. All measures were normally distributed as determined by Kolmogorov-Smirnov test. Pearson correlation test was used to estimate the relationship between BMD and each lipid profile component (CHOL, LDL, HDL, and TG).

Since both serum lipids and BMD were significantly related to BMI/smoking, the relationship between serum lipids and BMD was reassessed after adjusting for each variable using partial correlation test. Multivariable-adjusted linear regression analysis was used to investigate serum lipids and BMD relationship after adjusting for BMI and smoking as cardiovascular risk factors. A P value less than 0.05 were considered significant.

Results

Blood samples were obtained from 158 people who were interviewed, six subjects were excluded for abnormal laboratory results and 152 were included. They were 66 males (43.4%) and 86 females (56.6%). Mean ± SD for age was 35.55 ± 9.8 years, and for BMI was 26.27 ± 5.05 Kg/m^2. Participants' characteristics are summarized in Table 1.

Comparison between dyslipidemic and normal lipid profile groups BMD

BMD means of each measured skeletal site were compared between normal lipid profile subjects (n=61) and dyslipidemic subjects (n=91) using independent T-test.

BMD means of total lumbar spine femoral neck, and total hip in dyslipidemic group were higher than in normal lipid profile group.

	Females	Males	All
	N=86	N=66	N=152
Parameter	Mean ± SD	Mean ± SD	Mean ± SD
Age (years)	37.4 ± 9.99	33.14 ± 9.06	35.55 ± 9.80
BMI (Kg/m2)	25.93 ± 5.93	26.72 ± 3.69	26.27 ± 5.05
SerumCholestero (mg/dl)	187.04 ± 36.67	180.43 ± 39.95	84.17 ± 38.141
Serum LDL (mg/dl)	122.88 ± 32.80	118.43 ± 34.77	120.95 ± 33.63
Serum HDL(mg/dl)	58.09 ± 14.17	46.39 ± 10.89	53.01 ± 14.07
Serum TG (mg/dl)	106.31 ± 58.16	139.86 ± 73.60	120.88 ± 67.19
Total Lumbar BMD (g/cm2)	0.9525 ± 0.1141	0.9335 ± 0.1218	0.9442 ± 0.1175
Neck Femoral BMD (g/cm2)	0.7653 ± 0.1160	0.8561 ± 0.1309	0.8047 ± 0.1303
Total Hip BMD (g/cm2)	0.8725 ± 0.1220	0.9813 ± 0.1183	0.9197 ± 0.1317
Smoking status	Non-smoker 115 (75.7%) Smokers: 37 (24.3%)		

Table 1: Characteristics of study participants. Abbreviations: SD: Standard Deviation; BMI: Body Mass Index; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; TG: Triglyceride; BMD: Bone Mineral Density.

Independent Samples Test	**Mean ± SD (g/cm2)**	**Mean ± SD (g/cm2)**	
	Normal lipid profile subjects	**Dyslipidemic subjects**	
Parameter	**N=61**	**N=91**	**P value**
Total Lumbar BMD	0.9347 ± 0.1188	0.9506 ± 0.1168	0.41
Neck Femoral BMD	0.7936 ± 0.1410	0.8122 ± 0.1229	0.4
Total Hip BMD	0.8979 ± 0.1418	0.9344 ± 0.1230	0.1
	Non-smoker	Smokers	
	N =115	N=37	
Total Lumbar BMD	0.9583 ± 0.1192	0.9005 ± 0.0167	0.008
Neck Femoral BMD	0.8031 ± 0.1339	0.8098 ± 0.1201	0.789
Total Hip BMD	0.9005 ± 0.1321	0.9295 ± 0.1317	0.607

Table 2: Comparing means of total lumber, neck femoral, and total hip BMD between normal lipid profile and dyslipidemic subjects, smokers and non-smokers.

However, this difference was not statistically significance. The same test was used to comber BMD between smokers and non-smokers. This showed that BMD means of total lumbar spine was significantly higher in non-smokers (P=0.008). For femoral neck and total hip, there was no statistically significance difference in BMD means between smokers and non-smokers (Table 2).

Relationships between lipid levels and BMD

The association between lipid profile (total cholesterol, LDL, HDL, and TG) and BMD at various skeletal sites (lumbar spine, femoral neck, and total hip) were explored using Pearson correlation test. No statistically significant relationships were found between any lipid component and BMD at any measured skeletal site (Table 3). Figure 1 showed an example of cholesterol correlation with BMD at total lumber and total hip.

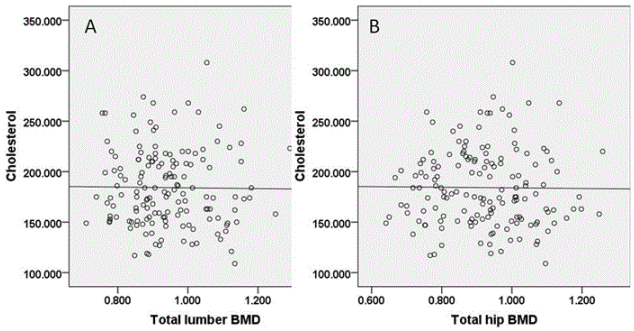

Figure 1: Correlation between lipid cholesterol and BMD (total lumber and total hip). Pearson correlation test: No statistically significant relationships between cholesterol and BMD at total lumber (A) and total hip (B).

A: Correlation coefficient (r)=-0.120, P=0.885

B: Correlation coefficient (r)=-0.011, P=0.896

Variables	**Total lumbar BMD**		**Femoral neck BMD**		**Total hip BMD**	
	r	P	R	P	r	P
Total cholesterol	-0.12	0.885	-0.055	0.503	-0.011	0.896
LDL	0.029	0.727	-0.023	0.779	0.047	0.569
HDL	0.004	0.962	-0.131	0.228	-0.162	0.135
TG	-0.078	0.338	0.065	0.429	0.154	0.058

Table 3: Correlation between lipid profile components and BMD (Pearson correlation test). r=Correlation coefficient.

Similar findings were found when investigation of correlation between lipid levels and BMD was repeated after grouping participants according to gender (Table 4).

The same results also were found when the relationship between lipid profile and BMD was reassessed after adjustment for BMI/smoking using Partial correlation test (Table 5).

Same results were obtained when the relationship between lipid profile components and BMD was re-evaluated after grouping participants according to age into two groups (<25 and ≥26 years) (data are not shown).This grouping was because peak bone mass is considered to be achieved between 18 and 25 years old [42].

Variable	Females		Males	
	r	P	r	P
Total lumbar BMD	0.054	0.612	-0.101	0.419
Femoral neck BMD	-0.089	0.415	0.04	0.751
Total hip BMD	-0.41	0.706	0.112	0.371

Table 4: Correlation between cholesterol and BMD in both genders (Pearson correlation test). r=Correlation coefficient.

Variables	Total lumbar BMD		Femoral neck BMD		Total hip BMD	
*	r	P	R	P	r	P
Cholesterol	-0.056	0.493	-0.095	0.244	-0.82	0.319
LDL	-0.046	0.575	-0.092	0.292	-0.07	0.394
HDL	0.104	0.204	-0.114	0.162	-0.165	0.043
TG	-167	0.041	-0.002	0.972	0.044	0.59
**	r	P	R	P	r	P
Cholesterol	0.064	0.432	-0.018	0.831	0.015	0.855
LDL	0.022	0.786	-0.005	0.954	0.044	0.59
HDL	0.02	0.811	-0.01	0.899	0.064	0.437
TG	-0.049	0.549	0.025	0.761	0.118	0.149

Table 5: Correlation between lipid profile components and BMD adjusted for BMI/smoking.

Discussion

Although bioactive lipoproteins role in pathogenesis of atherosclerosis is very well known, their effect on bone metabolism is less understood. Therefore many researchers tried to explore the relationship between lipid profile and BMD. Interestingly, contradict results were reported with absent [27-30] negative [31-35] or positive [36-38] relations.

We did not find any significant relationship between lipid profile and BMD in our participants who were Syrian premenopausal women and men younger than 50 years old.

Our results are consistent with that published by Solomon et al. in 2005 that showed no relation between lipid level and BMD [30]. Another study by Samelson et al. in 2004 also reported that total cholesterol levels did not have effect on osteoporosis occurrence in both genders [27]. Our findings are also consistent with that published by Jeong et al. in 2012 who found no relationship between total cholesterol, LDL and BMD in pre and postmenopausal Korean women, but they found positive relation between HDL and BMD of lumbar spine only in postmenopausal women [29].

However, our results disagree with studies that showed negative or positive relations between lipids and BMD [31-38]. This might be explained by the different inclusion criteria. Postmenopausal women and men older than 50 years were included in most of these studies. For instance Yamaguchi et al. found a negative relationship between lipid profile and BMD; their subjects were postmenopausal women [35]. On the other hand, Buizert et al. revealed a positive relation between lipid profile and BMD in postmenopausal women and men older than 55 years [38].

Makovey et al. in 2005 [43] suggested that estrogen might modify the inverse relationship between cholesterol, LDL and BMD. This might explain our results because all our participants were apparently healthy people aged 20-50 years so they are expected to have normal serum sex hormone levels which might affect the relationship between lipid profile and BMD.

In a recent review in 2014 [12], Tintut and L Demer said "relationship between BMD and lipid profile may be missed in studies that exclude subjects with cardiovascular disease, because if there is genetic susceptibility to tissue damage from hyperlipidemia, then the subjects who develop cardiovascular diseases from dyslipidemia may be the same individuals whose bone is vulnerable to dyslipidemia. Thus excluding subjects with hyperlipidemic heart disease may also exclude subjects with hyperlipidemic bone disease".

Taking this into consideration, we might have different results if we studied hyperlipidemic cardiovascular patients, because they would be expected to have hyperlipidemic bone disease. However, adjusting for cardiovascular risk factors such as gender, BMI and smoking did not affect our results. This disagrees with Kim et al. study in 2013 which concluded that BMD was inversely correlated with parameters of atherogenic dyslipidemia in South Korean men [44].

In conclusion the results of this pilot study do not support the hypothesis that there is an association between lipid profile and BMD. However, with our small sample size we cannot generalize this result in Syria. Further studies are required to investigate this relationship in large sample size with different age groups such as postmenopausal women, men older than 50 years. Hyper-lipidemic cardiovascular patients might give different results if they are included in the future.

Future work

Our plan is to re-evaluate study subjects after five years to address the long term effect of lipid profile on BMD.

Limitations

There were several limitations in our study. Firstly, we did not assess participants' physical activity or daily calcium and vitamin D intake which might affect BMD and consequently affect our results. Secondly, we excluded postmenopausal women and men older than 50 years. Finally, this is a pilot study with small sample size, so it is difficult to generalize our results on all Syrian population. However, this is a novel study as it is the first one that addressed lipid profile debatable relationship with BMD in Syria.

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