International Invention Journal of Medicine and Medical Sciences (ISSN: 2408-7246) Vol. 2(11) pp. 172-180, November, 2015
Available online http://internationalinventjournals.org/journals/IIJMMS

Full Length Research Paper

Impact of high serum lipid levels and ectopic fat mass on bone density in obese and non-obese hyperlipidemic middle age women

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Abstract

The aim of the study is to assess the relation between bone density and high serum lipid level status, to determine the contribution of fat mass to osteoporosis and the role of obesity associated with high fat content in osteoporosis. The study design was case control study. One hundred women of middle age ranged from (37 – 47 years) with normal menstrual cycle divided into two groups. Group I included 50 hyperlipidemic obese (HL-O) women and group Π included 50 hyperlipidemic non-obese (HL-NO) women of the same age. All these middle age women were suffering from hyperlipidemic disease with duration from 3 to 5 years, presented with rheumatological manifestations of hyperlipidemia, any symptoms of osteoporosis in the form of neck pain, low back pain, loss of height overtime, stopped posture and any debilitating pain of hips and wrists. Those with cardiovascular disease, diabetes, secondary osteoporosis caused by number of endocrine diseases, systemic diseases and who took drugs influence the bone metabolism and all other causes of osteoporosis were excluded from the study. Blood samples were taken to measure serum lipids Triglyceride (TG), Total Cholesterol (TC), High-Density Lipoprotein (HDL), and Low-Density Lipoprotein (LDL), bone biomarkers (bone alkaline phosphatase (BALP) and osteocalcin). Bone Mineral Density (BMD) at multiple skeletal sites was assessed by Dual-energy X-ray absorptiometry (DXA). Obesity was assessed by measuring body mass index (BMI) >30 kg/m^2 with normal waist circumference is <88 cm, values were estimated according to WHO criteria. Also ectopic fat mass was assessed clinically. Partial correlation analysis was used to evaluate the relationships between mentioned measurements after adjustment for weight and age. Contribution of fat mass to bone density and the risk of osteoporosis was also assessed. After adjustment for age, weight, height, and BMI, the correlation between serum lipids and BMD was assessed. The effect of lipids on bone biomarkers was evaluated as well. We found a positive correlation between HDL and lumbar spine BMD. Furthermore, we did not find any significant effect of serum lipids on BALP. The results are interesting as the positive effect of serum lipids specially TG, low HDL and high LDL on long bone BMD (osteoporosis and osteopenia through mechanisms which are not merely mediated by pathways in which bone biomarkers' alterations are involved. TC and LDL were not related to BMD.

Keywords: Bone density, Hyperlipidemia, Middle aged, Menstrual women.

INTRODUCTION

Osteoporosis is a disorder of the skeletal system characterized by reduced bone strength that increases the risk for fracture (Hodgson and Watts, 2003). Bone strength incorporates factors of both bone density and bone quality. Bone density is the volume of bone, whereas bone quality refers to the rate of turnover, bone architecture, mineralization, and accumulated damage. There are two types of osteoporosis: primary and secondary (Dawson-Hughes et al., 2008).

Women with osteoporosis are at increased risk for

fracture. Interestingly, fracture rates are even higher among women with osteopenia. Although osteoporosis and osteopenia by themselves are painless and not functionally problematic, the risk for fractures puts a patient at significant risk. Following a hip fracture, there is a 10% to 20% increase in mortality. Among survivors, 30% to 40% sustain some degree of permanent disability and 24% to 50% never return to independent living (Hodgson and Watts, 2003; Dawson-Hughes et al., 2008).

Obesity and osteoporosis are important global health problems with an increasing prevalence and a high impact on both mortality and morbidity.During recent decades, both diseases became a major health threat worldwide. Age and female gender increase the risk of developing both obesity and osteoporosis, which affect millions of women (Kado et al., 2004).

Perimenopausal women often show increased body weight, due to decrease in basal metabolism, alteration of hormonal levels, and reduced physical activity (Cagnacci et al., 2007).

Furthermore, estrogens may be inversely related to serum levels of homocysteine and lipids especially oxidized low density lipoprotein (LDL) (Zhao et al., 2008).

The association between obesity and osteoporosis has been actively investigated from epidemiological, clinical, and basic research points of view, and common pathophysiological links have been proposed, both obesity and osteoporosis are influenced by genetic and environmental factors, or the interaction between them; aging is associated with both diseases and with a high incidence of bone loss and bone marrow adiposity; bone remodeling and adiposity are both regulated via a complex interplay of adipokines and hormones; and adipocytes and osteoblasts derive from a common progenitor i.e. the mesenchymal stem cell (Zhu et al., 2000).

Extensive data have shown that, healthy pre-menopausal and postmenopausal women, have total body fat positively related to bone mineral density, an important and measurable determinant of fracture risk,[7-8] and that high body weight (or body mass index) is correlated with high bone mineral density, and that decreased body weight leads to bone loss (Felson et al., 1993; Ravn et al., 1999).

Fat mass, the most important index of obesity, has been demonstrated to have a similarly beneficial effect, leading to an increase in bone mass (Khosla et al., 1996).

Lipids have been shown to accumulate in bone and around bone vessels in patients with osteoporosis (Rajendran et al., 1995). Because the immature osteoblasts are located immediately adjacent to the subendothelial matrix of bone vessels, lipid accumulation in subendothelial matrix would be expected to inhibit differentiation of the bone-forming cells. In addition, because oxidized lipids induce endothelial expression of monocyte chemotactic a potent inducer of osteoclastic differentiation, oxidized lipids would be expected to promote bone resorption by recruitment and differentiation of osteoclast precursor cells. Consistent with this possibility, high-fat diet inhibits bone growth in chickens and the effect is reversed by antioxidants (Xu et al., 1995).

Clinical studies also support a role for lipids in osteoporosis (Mundy et al., 1999). Lipid-lowering agents also enhance bone mineralization. And may reduce osteoporotic fractures (Edwards et al., 2000: Chan et al., 2000).

Osteoporotic middle aged menstrual women are at significantly greater risk for cardiovascular disease than age matched controls. Patients with lower bone density and osteoporosis also have higher lipid levels, more severe coronary atherosclerosis, and have a greater risk of stroke death. The common finding of simultaneous vascular calcification and osteoporosis in individual patients suggests that local tissue factors govern regulation of biomineralization (Parhami et al., 2000).

Prevention is a key factor in osteoporosis management. For perimenopausal and postmenopausal women, prevention strategies focus on the following considerations:

Adequate intake of calcium (1000 mg/day for premenopausal women and postmenopausal women on hormonal therapy (HT), 1200 mg/day for perimenopausal or premenopausal women older than 50 years,1500 mg/day for postmenopausal women not taking HT and women older than 65 years. Adequate intake of vitamin D (400–800 international units/day). Weight bearing and resistance exercise. Fall prevention. Avoiding tobacco. Moderating alcohol intake (NIH, 1994).

Research question and objective

The research question for the purpose of this study is: ‘What is the role of lipids in osteoporosis in middle aged menstrual women, with the relation of obesity to osteoporosis?’

The objective of the study is to assess the relation between bone density and high serum lipid level status, determine the contribution of fat mass to osteoporosis and estimate the risk of osteoporosis in relation to body weight in middle age women.

MATERIAL AND METHODS

Research method and design

This is a case control study carried out at Department of Rheumatology in corporation with, Gynecology Departments out patient’s clinics and radiology department at Elamady hospital Doha Qatar. During the

period from 1st of December 2012 till the end of November 2014.

All patients received adequate information about the study and written consents were obtained before enrollment. The protocol was approved by the ethics committee of the hospital.

Study sample

The study participants included 100 women in the middle age ranged from (37 – 47 years) with normal menstrual cycle divided into two groups:
Group 1(HL-O):50 hyperlipidemic obese women.
Group II (HL-NO):50 hyperlipidemicnon- obese women.
The eligibility criteria were:
1. Middle aged (age ranged from (37 – 47 years)
2. Menstruating women
3. Hyperlipidemiais defined as serum total cholesterol >240 mg/dL, and/or serum triglyceride >135 mg/dl and/ or LDL>160 mg/dL, and/or HDL< 40mg/dl which is significant independent risk factor.

Exclusion criteria

1. Pregnancy
2. Lactation,
3. Postmenopausal women
4. Recent fracture,
5. Patients with history of diabetes, cardiovascular disease including coronary artery diseases, cancer, endocrinology disease and acute infection,
6. Use of special medications such as glucocorticoid, hormones, thyroid hormones, anticonvulsive drugs, heparin, aluminum containing antacids, lithium, omega-3 fatty acids, or other nutrients supplements,
7. Secondary osteoporosis caused by systemic diseases and who took drugs influence the bone metabolism and all other causes of osteoporosis.
8. Smoking or alcohol consumption.
9. Patients with spinal implant that involved lumbar vertebrae.

Anthropometric Measurements

Patients' demographic characteristics including age were obtained during face-to-face interviews. Body weight was measured, body height was obtained by measuring the supine length, and body mass index (BMI) was calculated as body weight (in kilograms) divided by height (in meters) squared.

The obesity is defined as body mass index > 30 kg/m2and waist circumference was measured by positioning the measuring tape midway between the top of hip bone and the bottom of rib cage, the normal value for women is < 88cm values were estimated according to WHO criteria (1994).

Laboratory Measurements

Blood samples were collected and centrifuged at 3000 rpm for 10 minutes at 4°C. Single session analysis was used to reduce interassay variation in serum samples. Samples were sent to laboratory for analysis and were frozen immediately. Serums HDL, LDL, total cholesterol (TC), and total triglyceride (TG) were measured via routine methods (Medica EasyRA Chemistry Analyzer Flags).Bone Alkaline Phosphatase (BALP) were measured by bone-specific alkaline phosphatase (BALP) ELISA kit (Medica EasyRA Chemistry Analyzer Flags) with detection range of 5-24.4ug/L. Serum ostecalcin was measured via (Synlab Weiden, kit: M-MID Osteocalcin, equipment E171, Roche Diagnostics) with normal range (14-46ng/ml). Also, fasting and post prandial blood sugar, glycosylated hemoglobin were measured.

Bone Mineral Density Measurements

The diagnosis of osteoporosis was done by using Dual energy X-ray absorptiometry scan (DEXA) that measure bone density in lumbar spine and left hip according to WHO definition, normal bone density is present when T score is – 1.0 or above, in osteopenia T score is between – 1.0 and – 2.5, in osteoporosis the T score is 2.5 standard deviation below the mean for young and in sever osteoporosis accompanied with fractures T score ≤ - 2.5 (Reid, 2002; Hammoudeh and Zirie, 2007).

Statistical analysis

All statistical analysis was performed by SPSS version 21 (IBM Corporation). The normality of data was first tested with one sam Kolmogorov-Smirnov test. Qualitative data were described using number and percent. Association between categorical variables was tested using Chi- square test. Continuous variables were presented as mean ± SD (standard deviation) for parametric data and Median for non-parametric data. The two groups were compared with Student *t* test (parametric data) and Mann-Whitney test (non parametric data). ANOVA test was used to compare mean of more than 2 groups. The relationship between lipid profile indexes and anthropometric variables (age, weight and BMI) were assessed by simple linear regression. The association between BMD in the spine, left hip and lipids was evaluated using partial correlation with adjustment for weight, height, BMI, and age. *P* value < 0.05 was considered

statistically significant.

Ethical Aspects

The protocol for the study was approved by the Ethical and Research Committee of the Hospital. Data were collected only after the informed consent had been signed by all patients.

RESULTS

Basic characteristics of these patients are summarized in Table (1) which revealed significant difference (P≤ 0.05) between fat mass, total cholesterol and triglyceride levels in both groups .while there were high significant differences(P≤.001) between total body weight, BMI, LDL and BALP in both groups. No significant difference between age, height, osteocalcin, HDL and BMD (t-score) in left hip and lumbar spine in both groups.

As regard BMD our results revealed osteoporosis in 3 patients(group) and osteopenia in 19 patients(10groupl,9 group) (table 4) in relation to patients characteristics analysis showed there was significant relation for age and BMI, high significant relation for weight, fat mass, triglyceride ,low BALP and osteocalcin (tables 2,3).

The primary analysis of demographics including age, weight, height, and BMI on serum lipids showed that there is a significant negative association between weight and HDL (P: 0.002, $r = -0.32$) and also between weight BMI and TG as well as LDL and BALP ($P < 0.0001$, $r = -0.38$ and $P < 0.0001$, $r = -0.36$, respectively). TG low HDL and high LDL was related to negative effect on BMD (table 3).

The existence of these statistically significant relationships defines these mentioned factors as confounder. Significant differences in all reported covariates were found among both groups. Age, weight, height, BMI, BMD, bone biomarkers, and body composition status differed significantly among both groups (P < 0.01).

After adjustment for age, weight, height, and BMI, the correlation between serum lipids and BMD was assessed. The effect of lipids on bone biomarkers was evaluated as well. We found a positive correlation between HDL and lumbar spine BMD (table 5). Furthermore, we did not find any significant effect of serum lipids on BALP (Table 3). The results are interesting as the positive effect of serum lipids specially TG, low HDL and high LDL on long bone BMD (osteoporosis and osteopenia) (table 3) through mechanisms which are not merely mediated by pathways in which bone biomarkers' alterations are involved.

The results reported here are consistent with the long held belief that subjects having larger body weight tend to have higher bone mass. When bone mass was adjusted for body weight, lean mass was consistently positively correlated with weight-adjusted bone mass (p<0.05), suggesting that the effects of lean mass on bone mass are not simply due to its weight. Most interestingly, fat mass was inversely associated with weight-adjusted bone mass (p<0.01) (Table 6), suggesting that higher fat mass does not increase bone mass when the mechanical loading effects of overall body weight are statistically controlled.

DISCUSSION

Extensive data have shown that, healthy pre-menopausal and postmenopausal women, have total body fat positively related to bone mineral density, an important and measurable determinant of fracture risk (Cummings et al., 1993; Melton et al., 1993) and that high body weight (or body mass index) is correlated with high bone mineral density, and that decreased body weight leads to bone loss (Felson et al., 1993; Ravn et al., 1999).

Fat mass, the most important index of obesity, has been demonstrated to have a similarly beneficial effect, leading to an increase in bone mass (Khosla et al., 1996).

Although data indicate that obesity exerts a protective effect on bone tissue, more recent studies have described an opposite event. In particular, although cross-sectional and longitudinal studies have shown that bone mass is positively related to body weight and body mass index, there are controversial issues as to whether lean mass or fat mass might be the most important determinant of bone mineral density (Sabour et al., 2014), yet the evidence suggests an inverse relationship between obesity and osteoporosis depending on how obesity is defined (Sabour et al., 2014). In the studies where obesity is defined on the basis of body mass index or body weight, obesity appears to act as a protective factor against bone loss and fractures; however, if obesity is considered as a percentage of body fat and distribution, as in the study published by Zhao et al. 2008 in a Chinese population, it becomes a risk factor for osteoporosis.

In our study, we aimed to assess the impact of lipids on osteoporosis in middle aged menstrual women by assessing correlations between bone biomarkers and lipid profile.

Clinical studies also support a role for lipids in osteoporosis(Mundy et al., 1999). Lipid-lowering agents also enhance bone mineralization and may reduce osteoporotic fractures (Edwards et al., 2000; Chan et al., 2000).

In our study weight was positively related to TG (P: 0.003, $r = 0.31$). BMI was correlated with LDL (P: 0.024, $r = 0.24$), TG (P: 0.007, $r = 0.29$), and HDL (P: 0.009, $r = -0.28$), results, showed in our study that

Table 1. Baseline characteristics of both groups (means and standard deviation) and differences of basic features among studied subjects (*n*: 100).

Items	Group I Hyperlipdemicobese(HL-O) (n=50)	Group II hyperlipdemic Non-obese(HL-NO) (n=50)	Test of sig.	p-value
Age (year)	41.22±2.92	41.10±2.65	t=.215	p=.830
height cm.	165.82±6.33	163.56±5.74	t= 1.86	p=.065
Weight kg	109.94±11.47	59.86±10.24	t= 23.02	p=≤.001**
BMI kg/m²	35.96±3.49	23.03±2.91	t= 20.11	p=≤.001**
Fat Mass (kg)	14.5±3.4	8.1±1.4	t=2 .9	p=.01*
TC	257.76±24.64	241.54±24.68	t= 3.28	p=.001*
TG	163.50±17.37	157.19±8.89	t=2.28	p=.024*
HDL	40.16±7.76	42.32±8.82	t=1.29	p=.197
LDL	176.77±32.81	151.45±15.07	t=4.95	p=≤.001**
BALP µg/L	10.36±4.93	6.77±1.60	t= 4.89	p=≤.001**
Osteo-calcin ng/ml	15.21±2.72	15.42±2.90	t= .374	p=.709
BMD of left hip (*T*-score)	-0.75 (-2.70-0)	-0.89 (-2-0)	Z= 1.42	p=.154
BMD of lumbar spine (*T*- score)	-0.83 (-2.76-0)	-0.94(-2.04: -0.04)	Z= 1.06	p=.285

TC=Total cholesterol, TG=Triglyceride, HDL=High Density Lipoprotein, LDL=Low Density Lipoprotein, BALP=Bone Alkaline Phosphatase, BMD= Bone Mineral Density.

Table 2. Relation between study groups and BMD (osteoporosis and osteopenia)

Items	Osteoporosis (n=3)	Osteopenia (n=19)	Normal (n= 78)	Test of sig.	p-value
Age	37.66±0.57[a]	40.68±2.94	41.41±2.69 [a]	F= 3.095	p=.05*
height cm.	178.66±1.15[a]	171.36±5.86[b]	166.56±8.82 [ab]	F=5.241	p=.007
Weight kg	138.33±1.15 [ab]	93.47±24.09 [ac]	80.75±26.12[bc]	F=8.70	p=≤.001**
BMI kg/m²	43.34±0.91 [ab]	31.45±6.48 [a]	28.48±6.94[b]	F= 7.88	p=.001*
Fat Mass cm.	91±0.86 [a]	92.14±2.21 [b]	77.98±15.24 [ab]	F=9.084	p=≤.001**
Normal	0(0%)	0(0%)	61(78.2%)	X^2= 44.11	p=≤.001**
Obese	3(100%)	19(100%)			

F for ANOVA test
Groups with similar superscript letters are statistically significantly different according to the Tukey HSD test (p≤0.05).

Table 3. Relation between serum lipids, bone biomarkars, osteocalcin and BMD (osteoporosis and osteopenia) in both groups.

Items	Osteoporosis (n=3)	Osteopenia (n=19)	Normal (n= 78)	Test of sig.	p-value
TC	256.67±5.77	240.11±58.68	233.68±35.10	F= .620	p=.540
Hyperlipdemia (>240)	3(100%)	17(89.5%)	65(83.3%)	X^2=.998	p=.607
TG	191.67±1.44 [ab]	165.05±15.44 [ac]	158±12.26 [bc]	F= 11.58	p=≤.001**
Hyperlipedmic (>135)	3(100%)	19(100%)	78(100%)	-	
HDL	61±0.86	105.08±56.59	102.88±62.22	F= .720	p=.489
>40 low risky	0(0%)	1(5.3%)	37(47.4%)	X^2=13.42	p=.001
<40	3(100%)	18(94.7%)	41(52.6%)		
LDL	166.67±2.88	117.01±53.49	108.79±79.85	F=.916	p=.404
Normal	0(0%)	10(52.6%)	50(64.1%)	X^2=5.47	p=.065
high	3(100%)	9(47.4%)	28(35.9%)		
BALP µg/L	5.16±0.11	6.35±1.71 [b]	9.24±4.30 [ab]	F=5.364	p=.006*
Normal (5.2-24.4)	1(33.3%)	14(73.7%)	77(98.7%)	X^2=27.47	p=≤.001**
Low <5.2	2(66.7%)	5(26.3%)	1(1.3%)		
Osteo-calcin ng/ml	12±0.52 [a]	11.87±0.77 [b]	16.28±2.37 [a b]	F=35.88	p=≤.001**

F for ANOVA test
Groups with similar superscript letters are statistically significantly different according to the Tukey HSD test (p≤0.05).

Table 4. Show the numbers and percentages of low bone density cases with comparison of T score in both groups

Category	Group I (HL-O) No = 50 Mean (Standard Deviation)			Group II (HL-NO) No = 50 Mean (Standard Deviation)		
Number and percentages of low bone density cases at lumbar spine and left hip	Lumbar spine	Left hip	Total number and %of lumbar spine & left hip	Lumbar spine	Left hip	Total number and % of lumbar spine & left hip
Osteoporosis	No(%)	No(%)	No(%)	No(%)	No(%)	0%
	2	1	3	0	0	
	4%	2%	6	0%	0%	
Osteopenia	4	6	10	3	6	9
	8	12	20	6	12	18
BMD of lumbar spine	−2.29 (0.94)			−2.16 (0.95)		
BMD of left hip	−2.11 (0.73)			−1.92 (0.74)		

Table 5. The relationship between serum lipids and bone mineral density in hyperlipidic middle aged menstrual obese women (Group I).

Category		G I (HL-O) (*n*:50)			
		TG	**TC**	**HDL**	**LDL**
BMD of lumbar spine	*T*-score	0.17	0.84	0.004** (*r* = 0.33)	0.42
BMD of left hip	*T*-score	0.36	0.42	0.09	0.85
Bone alkaline phosphatase		0.76	0.65	0.92	0.40

r = correlation coefficient Significance at level of $P < 0.05$

Table 6. Pearson correlations between fat mass and weight-adjusted bone area in GIO and GIINO.

		Lumbar Spine bone area	**Left hip bone area**	**total body bone area**
Fat mass (kg)	GIO	−0.25**	−0.16**	−0.22**
	GIINO	−0.17**	−0.12**	−0.15**

**Note: p<0.01.Fat mass was *negatively* correlated with weight-adjusted bone area.

BMI was a strong positive indicator for BMD, going with these results, It was observed in few previous studies that the mean BMD was higher in obese than in non-obese subjects. Another study reported that BMI influences the rate of bone turn over in a negative manner (Adami et al., 2004).

Existence of a probable relationship between lipid profile and bone mineral density (BMD) was initially derived from reported results on statins' positive effect on BMD (Solomon et al., 2005).

The assumption of relationship between lipids and BMD was tested in two cohort studies and showed a significant positive association between BMD and low density lipoprotein (LDL) and total triglyceride (TG) while it was negatively correlated with high density lipoprotein (HDL) (Battaglino et al., 2012). However some other literatures showed no relationship between lipid profile and BMD (Jiang et al., 2006).

Osteoporosis occurs among middle aged menstrual hyperlipidemic women due to mechanical unloading (Sabour et al., 2014; Sivas et al., 2009) along with alterations in bone metabolism (Dennison et al., 2007).

To our knowledge, the effect of serum lipids on BMD in middle aged menstrual hyperlipidemic women is still unknown and mostly the assessed population was postmenopausal women (Bağış et al., 2002; Wong et al., 2001), which is a known population with higher risk of osteoporosis.

In this study, we investigated only middle aged menstrual hyperlipidemic women excluding postmenopausal women to omit the bias effect of postmenopause, aging and other osteoporosis related risk factors. Middle aged menstrual hyperlipidemic women also represent a sensitive population susceptible

to osteoporosis and evaluation of the correlation between lipids and BMD in these patients is the main purpose of this study.

Changes in bone mass are associated with alterations in bone biomarkers. Lipids may affect BMD through their influence on bone biomarkers. In this field there are some specific known biomarkers including osteocalcin, and bone alkaline phosphatase (BALP) (Krum et al., 1992).

Solomon et al. 2005 found no association between serum lipids and BMD. This study is noticeable by considering its sample size. However, these relationships may be different in individuals with background diseases or medical conditions that are known to be associated with osteoporosis. Here, we found that lumbar spine BMD was positively related to low HDL, high LDL and TG. Previously Dennison et al. 2007 showed a negative correlation between HDL and femoral BMD in healthy individuals which contradicts with our results.

Wong et al. 2001 illustrated the effect of injury level on lipid profile and their study showed higher level of TC among patients with injury at lumbar level. Our results contradicts with Wong's study (Tankó et al., (2003). The negative correlation between HDL and BMD which was reported in mentioned studies does not lead to increased BMD as a consequence of various factors including mechanical unloading and changes in bone metabolism. As a result we do observe such a negative association between only low HDL and BMD. The controversial results in different study populations suggest that lipids' relationship with BMD is manipulated by many various factors and, apart from background medical condition, factors like lifestyle, physical activity, and amount of fat mass should be considered. Most studies found no association between TC and BMD in various populations (Wu et al., 2003; Parhami et al., 2002; Pliatsika et al., 2012). which is in agreement with our results. However, while Parhami et al. 2002 illustrated that baseline level of cholesterol synthesis is necessary for the osteoblastic differentiation, it seems that total cholesterol does not directly affect BMD. Here, we report the same findings.

LDL was also not related to BMD which is in agreement with Dennison's 2007 report in general population. Many studies do not support strong association between lipids' concentrations and bone mass measurements (Tothill et al., 1997). In this study, we report also a weak relationship between lipid levels and BMD in hyperlipidic middle aged menstrual women; Only HDL was positively associated with lumbar spine BMD. LDL and TC levels revealed no influence on BMD.

It should be noted that the statistically significant correlations reported here only imply an overall effect of the shared factors in determination of fat and bone mass. Some individual factors may not follow this correlation.

An additional concern with our study is that the observed negative correlation between fat mass and weight-adjusted bone mass might be an artifact caused by dual energy x-ray absorptiometry (DXA) measurement. It is likely that heterogeneous distributions of soft tissues could lead to systematic inaccuracies inherent to DXA-derived BMD measurements. Changes of fat distribution can cause alterations in bone measurement without any real change in the skeleton (Bolotin, 1998; Pino et al., 1991). However, in our study, they are not likely to be biased for the following reasons:

1. A previous analytic and quantitative simulation study indicated that decreasing fat mass by weight change always artificially led to lower BMD, and *vice versa* (Susanto, 2011), which is qualitatively different from our results.

2. Prior studies (Bolotin, 1998; Pino et al., 1991). showed increasing fat thickness may decrease total body BMD. The spurious decrease in BMD, if due to DXA measurement, is attributable to the potential spurious increases in both bone mineral content(BMC) (numerator) and bone area (denominator for BMD) (Bolotin, 1998; Pino et al., 1991).

Regarding the correlation between serum osteocalcin level and obesity in both groups, result of this study found that serum osteocalcin level was positively correlated with obesity for both group, yet other similar published studies (Susanto, 2011) which showed increase serum osteocalcin level with aging.

Bone area may have a relatively larger spurious increase than BMC, resulting in a potential spurious decrease of BMD. However, in this study, we found a negative, rather than a positive, correlation between fat mass and weight-adjusted total body bone mineral content (TB BMC), which indicates that increasing fat mass is associated with a smaller bone mineral content (BMC). This result suggests that our finding is unlikely to be explained by an artifact of the DXA measurement, which leads to larger BMC with increasing fat. Moreover, we tested the relationship between fat mass and bone area in our two study groups. We found that fat mass was *negatively* correlated with weight-adjusted bone area (Table 6). This finding is qualitatively different from the positive correlation between spurious change of bone area and change of fat thickness due to DXA measurements as suggested in earlier studies (Zhao et al., 2007). This result further ensured the robustness of our results against the potential artificial effects of DXA measurement.

In summary, we found a negative correlation between fat mass (or Percentage Fat Mass PFM) and bone mass. In addition, we reaffirmed the beneficial effects of increased estrogen synthesis by fat tissue in obese women, has been suggested as one of the potential mechanisms for the protective effect of fat mass on bone.

Study limitations

Some of the limitations of our study is possibility of a selection bias could limit the generalizability of the findings of the study. Also, our study is cross-sectional in nature instead of a longitudinal design. Therefore, in this study, the relationship between bone mass and obesity-related variables is descriptive and might be confounded by cohort effects. However, the age range of our sample is narrow, which may suggest that cohort effects, if any, may be relatively small.

CONCLUSIONS

In summary, we have found that an association between BMD and serum lipid levels, yet the relationship between serum lipids and BMD in hyperlipidic middle aged menstrual women; is weak. This study shows a positive correlation between HDL and lumbar spine bone mineral density (BMD) and a negative association between HDL, TG and LDL and bone markers in hyperlipidic middle aged menstrual women TC was not related to BMD and bone biomarkers. This association suggests skeletal site-specificity differences in terms of the effects of serum lipids on BMDs at various skeletal sites.

From our study, we concluded that in obese women, increased estrogen synthesis by fat tissue has been suggested as one of the potential mechanisms for the protective effect of fat mass on bone, even though there are data indicating that women with high body mass index are protected from osteoporosis, increasing evidence seems to show conflicting results regarding this issue, suggesting that obesity might actually interfere with bone health. In particular, the relationship between obesity and osteoporosis depends on how obesity is defined. If obesity is defined on the basis of body mass index or body weight, it appears to protect against bone loss and osteoporosis. However, if obesity is based on the percentage of body fat, it may be a risk factor for osteoporosis.

RECOMMENDATIONS BASED ON OUR STUDY

1- Osteoporosis should be apriority among public health professionals, health care providers and decision makers.
2- All health professionals need to overcome effectively market the risk of and prevention strategies for osteoporosis.
Future studies are needed to determine whether degree and duration of hyperlipidemia correlate with osteoporosis in hyperlipidic middle aged menstrual women; whether experimental hyperlipidemia affects bone density in animals; and whether the degree of lipid lowering determines the degree of reduction in osteoporosis.
3- Existence of the interaction between adiposity and bone, elucidation of this relationship will generate substantial research and studies using molecular and genetic methodology to help identify regulatory pathways that lead to the development of therapeutic interventions that can be used to treat osteoporosis and obesity.
4- Randomized trials with adequate power are needed to assess bone density and fracture in osteoprosis in hyperlipidic middle aged menstrual women
5- A critical priority is to determine whether treatments for osteoporosis aggravate or benefit vascular calcification and vice versa. The fundamental mechanisms by which lipids modulate differentiation of mineralizing cells and biomineralization must be evaluated and known mechanisms by which lipids regulate atherogenesis offer a valuable starting point.
6- Existing and exciting new animal models offer promise in identifying genetic regulatory factors of osteoprosis in hyperlipidic middle aged menstrual women
7- Research priorities should lead to new and efficient strategies for simultaneous biologic reversal of both osteoporosis and hyperlipidia in middle aged menstrual women.

ACKNOWLEDGEMENTS

We wish to express profound gratitude to the staff of Department of rheumatology in corporation with, Gynecology and Obstetrics out patient's clinics and radiology department at Elamady hospital Doha Qatar for their immense support during the completion processes of our study.

Conflict of Interest

The authors declare no conflict of interest.

Abbreviations

BALP: Bone alkaline phosphatase
BMC Bone Mineral Content
BMD: Bone mineral density
BMI: Body mass index
DXA: Dual-energy X-ray absorptiometry
HDL: High density lipoprotein
LDL: Low density lipoprotein
PFM: Percentage Fat Mass
TB BMC: Total Body Bone Mineral Content
TC: Total cholesterol
TG: Triglyceride.
*r= correlation coefficient.

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How to cite this article: Ashraf EA, Alsaeed Elsayed AAA, Hossam Ibrahim AE (2015). Impact of high serum lipid levels and ectopic fat mass on bone density in obese and non-obese hyperlipidemic middle age women. Int. Inv. J. Med. Med. Sci. Vol. 2(11): 172-180