Clinical Rheumatology (2019) 38:739–747
https://doi.org/10.1007/s10067-018-4343-4

ORIGINAL ARTICLE

Clinical and body composition predictors of bone turnover and mineral content in obese postmenopausal women

Rim Cherif [1] · Feten Mahjoub [2] · Hela Sahli [3] · Elhem Cheour [3] · Mohsen Sakly [1] · Nebil Attia [1]

Received: 22 August 2018 / Revised: 4 October 2018 / Accepted: 15 October 2018 / Published online: 19 October 2018

Abstract

The purpose of this study was to determine the predictors of bone mineral density (BMD), bone mineral content (BMC), and bone turnover markers in obese postmenopausal women. In this cross-sectional study, 81 postmenopausal women aged 58.40 ± 6.08 years were analyzed. Anthropometric parameters were recorded. Serum glucose parameters, serum lipid profiles, adipokines, renal, hepatic parameters, and bone markers concentrations were determined by well-validated laboratory routine methods. BMD, BMC, and body composition were measured by Dual X-ray Absorptiometry. We found a significant correlation of BMD with age, years since menopause, anthropometric parameters, glycemia, alkaline phosphatase, fat mass, and lean mass. Multiple regression analysis demonstrated that years since menopause, waist circumference, alkaline phosphatase, trunk fat, and lean mass were independently associated to BMD. Also, age, years since menopause, anthropometric parameters, total cholesterol, alkaline phosphatase, fat mass, and lean mass were correlated to BMC. However, only waist circumference and trunk fat were independently related to BMC. Bone turnover markers were significantly correlated to the age, glycemia, HbA1c, adipokines, hepatic parameters, and lean mass. Nevertheless, only adipokines, gamma glutamyl transferase (GGT), and alkaline phosphatase were independently associated to bone turnover markers. These observations suggest that number of years since menopause, waist circumference, alkaline phosphatase, trunk fat, and lean mass were the only significant predictors of BMD. However, waist circumference seems to be a stronger predictor than trunk fat for BMC. Moreover, adiponectin, resistin, GGT, and alkaline phosphatase were significant predictors of the bone resorption (CTX-I) and the bone formation (P1NP) markers.

Keywords Body composition · Bone markers · Bone mineral content · Bone mineral density · Clinical parameters · Postmenopausal women

Introduction

Soon after menopause, the process of bone loss begins in women, due to increased numbers of osteoclasts and resorption lacunae in the skeleton which overcomes bone formation by osteoblasts [1]. Important unbalanced bone remodeling, leading to the loss of bone tissue, is observed in pathological conditions such as osteoporosis. Low bone mineral density (BMD) and alteration of bone quality are the main features of postmenopausal osteoporosis [2]. Moreover, age-related changes in the body composition, metabolic factors and hormonal deprivation after menopause, accompanied by a decrease in physical activity may all lead to the installation of several pathologies such as obesity, type 2 diabetes, and dyslipidemia. However, it is still not clear whether or not these diseases are related to osteoporosis and how they influence bone health.

There is a disagreement in the literature on the effect of obesity-, diabetes mellitus-, and dyslipidemia-related parameters on bone profile. Traditionally, obesity has been considered a protective factor for bone loss and osteoporosis, likely for the positive association of the body mass index and the waist circumference with the BMD [3]. However, more recent studies have described an opposite event and support the hypothesis of a negative effect of obesity on bone [4, 5].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10067-018-4343-4) contains supplementary material, which is available to authorized users.

✉ Rim Cherif
cherifrim17@yahoo.fr

1 UR11ES33, Research Unit Integrated Physiology, Laboratory of Biochemistry and Human Nutrition, Faculty of Sciences of Bizerte, Carthage University, 7021 Jarzouna, Tunis, Tunisia

2 Department of Diabetology, National Institute of Nutrition, Tunis, Tunisia

3 Immuno-Rheumatology Laboratory, Rabta Hospital, Faculty of Medicine of Tunis, Tunis El Manar University, Tunis, Tunisia

Body composition, another obesity-related parameter, has a strong impact on bone health. While there is little doubt that total mass has an effect on bone, whether it is the effect of fat mass or lean mass that influences bone is disputed. Some studies have indicated that lean mass, not fat mass, is associated with BMD [6, 7]. Other studies have demonstrated that fat mass, not lean mass, is an important determinant of BMD [8, 9].

Regarding biochemical parameters, previous epidemiological studies have demonstrated a relationship between serum lipid profiles and BMD [10, 11]. Furthermore, the question of whether the serum lipid profiles affect the value of BMD in postmenopausal women is unclear. Moreover, among laboratory parameters, there is a lack of information on the relationship between hepatic and renal parameters with bone and their associations are rarely studied in postmenopausal women.

The relationship between bone and type 2 diabetes has been known for many years. Indeed, some authors have reported elevated BMD [12] and low risk of osteoporosis [13], whereas some have reported decreased BMD [14], and other have reported that type 2 diabetes did not affect bone [15]. However, it is still not clear which parameter such as fasting glucose, insulinemia, and glycated hemoglobin has an effect on bone profiles.

Since the association between anthropometric, biochemical, and body composition parameters with bone-related parameters such as BMD, bone mineral content (BMC), and bone remodeling markers has not been assessed simultaneously in postmenopausal women, we aimed to investigate these relationships and identify predictor of bone health in postmenopausal women.

Materials and methods

Subjects

The design and method of this study have been detailed previously [16]. Briefly, the subjects in this study were 81 postmenopausal obese women with type 2 diabetes mellitus. We consecutively recruited subjects who visited the Endocrinology Department of the National Institute of Nutrition of Tunis, Tunisia, during visits for routine checkups. Participants were included if they were aged 50 or more, without spontaneous menses for more than 1 year and had no previous osteoporotic fracture or known diagnosis of osteoporosis. Women with liver or renal disease, inflammatory disease, parathyroid and thyroid, chronic inflammatory rheumatism, early natural menopause before age 40, and receiving medicine known to influence bone metabolism, such as corticosteroids, heparin, anticonvulsants, vitamin D or calcium supplementations, and bisphosphonates, were not included. Each patient completed a questionnaire designed to collect this information. The protocol of this study was approved by the local ethic committee of National Institute of Nutrition of Tunis and written informed consent was obtained from each participant.

Anthropometric measurements

Height was measured to the nearest 0.1 cm, and weight was recorded to the nearest 0.1 kg, while participants were wearing lightweight clothing and no shoes. BMI was calculated as weight (kg)/height (m^2). Waist circumference was measured to the nearest 0.1 cm at the umbilical level with the participant in a standing position.

Biochemical analysis

Blood samples were obtained from an antecubital vein after a fast of at least 12 h. The sample was taken at a fixed time in the morning between 07:30 and 8:30. Serum fasting blood glucose, glycated hemoglobin (HbA1c), lipid levels (total cholesterol, triglycerides, and high-density lipoprotein cholesterol [HDL cholesterol]), hepatic parameters (Alanine aminotransferase [ALAT], Aspartate aminotransferase [ASAT], Gamma glutamyl transferases [GGT], and alkaline phosphatase), creatinine, calcium, and phosphorus were determined by well-validated laboratory routine methods. Serum low-density lipoprotein cholesterol (LDL cholesterol) values were estimated using the Friedwald formula [17]. Serum insulin, adiponectin, and resistin were measured by enzyme-linked immunosorbent assay using the ALPCO kit (ALPCO kit, Salem, NH) for insulin and adiponectin and BioVendor kit (BioVendor kit, Brno, Czech Republic) for resistin. The homeostasis model assessment insulin index (HOMA-IR) was calculated using the following formula: Fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5 [18].

Dual energy X-ray absorptiometry (DXA) measurements

DXA scans were undertaken to assess BMD (in lumbar vertebrae L1–L4, left and right femur, total hip, left and right femoral neck, and the whole body), BMC (in the legs, trunk, and the whole body), and the body composition (fat and lean mass of the legs, trunk and the whole body) using a GE-Lunar PRODIGYTM device. The measurement results of BMD values were expressed in g/cm^2 and BMC and body composition values were expressed in grams. Annual servicing and calibration according to the manufacturer's specifications were carried out and daily quality control was performed by the measurement of a phantom supplied by the manufacturer. The coefficient of variation was 0.35% for the whole body BMD, 1.25% for the lumbar spine (L1–L4) BMD, 1.3% for the femoral neck BMD, 0.6% for lean body mass, and 2.5% body fat mass. These densitometry examinations of patients were realized at the Rheumatology Department of the Rabta Hospital of Tunis, Tunisia.

Statistical analysis

Statistical analysis was performed using the StatView package (Version 5, SAS Institute, Inc., Cary, NC). The characteristics of the patients are presented as mean ± standard deviation (SD). All variables were tested for normality using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Pearson's correlation test was performed to examine the association between bone-related parameters and clinical, biochemical, and body composition parameters. Multiple linear regression analysis with a subsequent backward procedure was used to reveal the independent predictor variables of bone-related parameters. Statistical significance level was set at $p < 0.05$.

Results

Characteristics of the population

A total of 81 postmenopausal women were observed and clinical, biochemical, and body composition data were detailed in Table A. The mean age (± SD) was 58.40 ± 6.08 years and the number of years since menopause was 10.79 ± 7.02 years.

Women in this study were obese and diabetic with an average of BMI of 33.36 ± 5.42 kg/m^2 and an average of fasting glucose of 10.89 ± 4.23 mmol/l.

Our population is characterized by a mean cholesterol level of 5.00 ± 1.40 mmol/l and an average of triglycerides of 1.62 ± 0.88 mmol/l. The phosphocalcic profile of these patients indicates an average calcium level of 2.27 ± 0.09 mmol/l and an average phosphoremia of 1.11 ± 0.13 mmol/l (Table A: supplementary material).

Table B shows the mean (± SD) of BMD in the different skeletal sites measured as well as the mean of BMC (in legs, trunk, and whole body) and bone markers (CTX-I and P1NP). The mean BMD was 1.08 ± 0.16 g/cm^2 at the L1–L4 lumbar spine, 1.01 ± 0.13 g/cm^2 at the total hip, and 1.15 ± 0.09 g/cm^2 in the whole body. The mean (± SD) of the whole body BMC was 2230.50 ± 348.65 g and the means of CTX-I and P1NP were 2346.21 ± 1953 pmol/l and 1346.61 ± 23.74 μg/l respectively (Table B: supplementary material).

Associations of bone mineral density with clinical and body composition parameters

A simple correlation analysis revealed that for all bone sites measured except the L1–L4 vertebrae, BMD correlates negatively and significantly with the age of the patients and the number of years since menopause.

Analysis of the correlation of anthropometric parameters with BMD shows that the weight correlates positively and significantly with BMD at all measured sites expect for L1–L4 vertebrae. Waist circumference correlates positively and significantly only with the whole body BMD ($r = 0.263$, $p < 0.05$). We also observed a positive and significant correlation of BMI with BMD at the right femur, total hip, and whole body ($r = 0.259$, $r = 0.258$, $r = 0.282$ respectively, $p < 0.05$). Only height correlates significantly with BMD at all measured sites. Among carbohydrate balance parameters, only serum glucose level correlates positively and significantly with BMD and this at the whole body ($r = 0.249$, $p < 0.05$). Glycated hemoglobin, serum insulin, and HOMA-IR were not related to BMD at any site.

Our results show that alkaline phosphatase correlates negatively and significantly with the BMD at all the measured sites. Regarding body composition, we have observed a significant and positive correlation of the trunk and whole body fat with BMD at different sites. Lean mass was also positively correlated to BMD at all sites and fat mass was not correlated to lumbar BMD. However, we found no correlation of BMD with adipocytokines, lipid, renal, and phosphocalcic parameters (Table 1).

Multiple linear regression analysis was performed to evaluate independent predictor of BMD. In this analysis, we only included parameters that correlated significantly with BMD in the simple correlation analysis. Through this analysis, we found a disappearance of the correlation of age with BMD. However, the number of years since menopause remains significantly and negatively correlated with BMD except for the whole body.

Also, multiple regression analysis demonstrated that waist circumference was the only anthropometric parameter that is significantly and independently associated with BMD and this at the lumbar vertebrae and the left femoral neck ($\beta = -0.415$; $\beta = -0.387$ respectively).

Association between alkaline phosphatase, trunk fat, lean mass parameters, and BMD persists after multiple regression analysis. However, fasting blood glucose and whole body fat are not independently related to BMD in the different measured sites (Table 2).

Associations of bone mineral content with clinical and body composition parameters

The age of patients and the number of years since menopause correlate negatively and significantly with the BMC of the legs and the whole body. However, these parameters do not correlate with the trunk BMC.

Legs BMC correlates positively with all anthropometric parameters. Trunk BMC correlates positively with height and negatively with waist circumference ($r = -0.304$, $p < 0.01$) and BMI ($r = -0.367$, $p < 0.001$). Only height correlates with the whole body BMC ($r = 0.611$, $p < 0.001$). Also, a negative and significant correlation was observed between BMC and alkaline phosphatase in all skeletal sites. Total cholesterol was negatively related to legs BMC only. However, we did not find any relation

Table 1 Correlation of bone mineral density with clinical and body composition parameters ($n = 81$)

	L-BMD	LF-BMD	RF-BMD	TH-BMD	LFN-BMD	RFN-BMD	WB-BMD
Age	− 0.172	− 0.352**	− 0.379**	− 0.369**	− 0.356**	− 0.404**	− 0.304*
Years since menopause	− 0.219	− 0.397**	− 0.419***	− 0.413***	− 0.421***	− 0.491***	− 0.226*
Weight	0.205	0.390**	0.362**	0.381***	0.232*	0.260*	0.450***
Height	0.435***	0.298*	0.225*	0.265*	0.382**	0.320*	0.365**
Waist circumference	− 0.047	0.193	0.202	0.200	0.002	0.073	0.263*
BMI	$-1.5.10^{-4}$	0.251	0.259*	0.258*	0.051	0.110	0.282*
Glycemia	0.079	0.146	0.135	0.142	0.124	0.087	0.249*
HbA1c	0.034	0.118	0.103	0.112	0.119	0.035	0.138
Serum insulin	0.045	0.149	0.076	0.115	0.056	0.025	0.006
HOMA-IR	0.020	0.168	0.107	0.140	0.074	0.028	0.059
Adiponectin	0.032	0.089	0.094	0.093	0.112	0.158	0.147
Resistin	− 0.004	− 0.014	0.015	0.002	− 0.049	− 0.014	− 0.028
Total cholesterol	0.063	− 0.026	− 0.006	− 0.016	0.001	0.039	− 0.119
HDL cholesterol	− 0.094	− 0.127	− 0.124	− 0.127	− 0.006	− 0.041	− 0.108
LDL cholesterol	0.134	− 0.073	− 0.084	− 0.080	− 0.101	− 0.099	− 0.056
Triglycerides	− 0.003	0.075	0.119	0.098	0.124	0.210	− 0.094
ASAT	0.059	0.078	0.062	0.071	0.095	0.070	0.004
ALAT	0.032	0.149	0.143	0.148	0.111	0.107	0.045
GGT	0.096	0.029	0.057	0.043	− 0.012	0.054	0.010
Alkaline phosphatase	− 0.324*	− 0.441***	− 0.426***	− 0.438***	− 0.473***	− 0.475***	− 0.351**
Creatinine	0.203	− 0.026	− 0.109	− 0.067	− 0.034	− 0.082	0.007
Calcium	0.024	− 0.145	− 0.224	− 0.186	− 0.023	− 0.087	− 0.194
Phosphorus	− 0.143	0.023	− 0.023	0.004	0.044	− 0.007	− 0.137
Leg fat	0.049	0.097	0.067	0.083	0.017	0.009	0.143
Trunk fat	0.162	0.381**	0.395**	0.392**	0.243*	0.284*	0.347**
Whole body fat	0.126	0.292**	0.286**	0.293**	0.144	0.171	0.302**
Leg lean	0.409***	0.451***	0.402***	0.432***	0.374***	0.363***	0.535***
Trunk lean	0.127	0.416***	0.404***	0.415***	0.277*	0.322**	0.540***
Whole body lean	0.282*	0.476***	0.444*	0.466***	0.339**	0.363**	0.608***

The results are expressed by the correlation coefficient of Pearson. Threshold of significance $p < 0.05$ (Pearson correlation test)

BMD-L lumbar bone mineral density (L1-L4), *LF* left femur, *RF* right femur, *TH* total hip, *LFN* left femoral neck, *RFN* right femoral neck, *WB* whole body, *BMI* body mass index, *HbA1c* glycated hemoglobin, *HOMA-IR* homeostasis model assessment insulin, *HDL cholesterol* high-density lipoprotein cholesterol, *LDL cholesterol* low-density lipoprotein cholesterol, *ALAT* alanine aminotransferase, *ASAT* aspartate aminotransferase, *GGT* gamma glutamyl transferases

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

between BMC and the other lipid parameters, glycemia, adipocytokine, renal, and phosphocalcic parameters.

In terms of body composition, there were positive associations between legs BMC and fat mass of the legs, the trunk, and the whole body ($r = 0.347$, $r = 0.388$, $r = 0.436$ respectively). Also, lean mass seems to be positively associated to legs and the whole body BMC and negatively associated to trunk BMC (Table 3).

The multiple linear regression analysis shows that the age of the patients and the number of years since menopause are not independently correlated with the BMC. Our results reveal that waist circumference is the only anthropometric parameter that is negatively and significantly related to leg ($\beta = -0.689$, $p < 0.01$), trunk ($\beta = -0.716$, $p < 0.01$), and the whole body BMC ($\beta = -0.896$, $p < 0.01$). In body composition parameters, only trunk fat was significantly and positively correlated to trunk BMC (Table 4).

Associations of bone markers with clinical and body composition parameters

A simple correlation analysis revealed that the age of women was significantly and positively correlated to both resorption bone marker (CTX-I) and formation bone marker (P1NP). The serum glucose level was negatively correlated to CTX-I ($r = -0.274$; $p < 0.05$) and P1NP ($r = -0.221$; $p < 0.05$). However, HbA1c was only related with CTX-I ($r = -0.283$;

Table 2 Multiple linear regression analysis of association between bone mineral density (dependent variable) and the measured parameters ($n = 81$)

	L-BMD	LF-BMD	RF-BMD	TH-BMD	LFN-BMD	RFN-BMD	WB-BMD
Age	0.145	0.059	0.011	0.036	0.049	0.014	0.019
Years since menopause	− 0.178	− 0.358*	− 0.379*	− 0.373*	− 0.364*	− 0.438**	− 0.143
Weight	0.281	0.853	0.534	0.707	0.409	0.438	0.045
Height	0.315	− 0.269	− 0.235	− 0.256	0.046	− 0.102	0.132
Waist circumference	− 0.415*	− 0.204	− 0.135	− 0.172	− 0.387*	− 0.197	− 0.181
BMI	− 0.012	− 0.651	− 0.421	− 0.546	− 0.274	− 0.399	0.054
Glycemia	0.034	0.093	0.088	0.092	0.061	0.024	0.176
Alkaline phosphatase	− 0.006	− 0.418***	− 0.330*	− 0.336*	− 0.266	− 0.275*	− 0.098
Trunk fat	0.220	0.439	0.561*	0.505*	0.482	0.497*	0.211
Whole body fat	− 0.088	− 0.426	− 0.062	− 0.138	− 0.350	− 0.395	− 0.153
Leg lean	0.338*	0.263	0.234	0.235	0.218	0.216	0.147
Trunk lean	− 0.159	0.386*	0.477*	0.452*	0.269	0.328	0.371*
Whole body lean	0.213	0.490	0.615*	0.411*	0.306	0.361	0.579*

The results are expressed by the standardized β coefficient. Threshold of significance is $p < 0.05$ (multiple linear regression test)

L-BMD lumbar bone mineral density (L1-L4), *LF* left femur, *RF* right femur, *TH* total hip, *LFN* left femoral neck, *RFN* right femoral neck, *WB* whole body, *BMI* body mass index

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

$p < 0.05$). In terms of adipocytokines, we have observed a negative correlation between adiponectin, CTX-I, and P1NP. Also, resistin correlated positively with the bone resorption marker ($r = 0.313$; $p < 0.01$). P1NP correlated significantly and positively with all the hepatic parameters; nevertheless, CTX-I was only correlated with alkaline phosphatase ($r = 0.511$; $p < 0.001$). We have also observed a negative correlation of legs lean mass and whole body lean mass with CTX-I ($r = -0.282$; $r = -0.244$; $p < 0.05$ respectively). But, we did not find any relation between bone markers and anthropometric parameters, lipid profiles and fat mass (Table 5).

Table 6 presents the results of multiple linear regression analysis for the predictor variable of bone markers. Our results demonstrate that adiponectin, GGT, and alkaline phosphatase were significant predictors of the bone formation marker P1NP. Also, this analysis indicated that CTX-I was independently related to adiponectin, resistin, and alkaline phosphatase (Table 6).

Discussion

The main purpose of this study was to explore associations of anthropometric, biochemical, and body composition parameters with BMD, BMC, and bone remodeling markers in order to identify predictors of bone health in postmenopausal women. We found that number of years since menopause, waist circumference, alkaline phosphatase, trunk fat, and lean mass were the only significant predictors of BMD. However, our results demonstrate that only waist circumference and trunk fat were independently and significantly associated to BMC. Moreover, adiponectin, resistin, gamma glutamyl transferases (GGT), and alkaline phosphatase were significant predictors of the bone resorption (CTX-I) and the bone formation (P1NP) markers.

It is well known that the age and number of years since menopause have a negative effect on bone mineral density and influence the health of bone. Elderly people experience bone loss with aging after peak bone mass. Indeed, several studies have demonstrated that there is a significant decrease in bone mass in women with menopause and the peak bone loss is reached at 50–54 years [19]. In our study, we report that age and age of menopause are negatively correlated to BMD in all measured sites except for the lumbar vertebrae. Similarly, Cui et al. have demonstrate a decrease in BMD with aging in postmenopausal women [20] and other studies have recorded a rapid decrease in BMD from 45 to 49 to 55–59 years [19]. We have also observed a negative correlation between BMC and the age but there is a lack of data in literature about the relationships between BMC and age. Furthermore, the sex steroid levels, including estrogen, rapidly decrease in postmenopausal women which lead to an accelerated phases of bone loss and an increase of bone turnover. Indeed, serum PINP and CTX-I increase at the menopause and then remain higher than before the menopause [21]. In accordance with this information, we have found a positive correlation between CTX-I and P1NP with age of women. However, after multiple linear regression analysis between age and bone parameters, the number of years since menopause was the only significant predictor of BMD.

Body mass index (BMI) is routinely used in epidemiological studies and clinical practice to classify adults as underweight, overweight, or obese, and studies evaluating the association between BMI and BMD have shown positive correlation [22]. Similarly, our finding demonstrates a significant positive

Table 3 Correlation of bone mineral content with clinical and body composition parameters ($n = 81$)

	Legs BMC	Trunk BMC	Whole body BMC
Age	− 0.302**	− 0.124	− 0.246*
Years since menopause	− 0.256*	− 0.182	− 0.216
Weight	0.562***	− 0.174	0.210
Height	0.687***	0.384***	0.611***
Waist circumference	0.263*	− 0.304**	− 0.032
BMI	0.241*	− 0.367***	− 0.087
Glycemia	0.187	0.022	0.160
HbA1c	0.100	0.013	0.087
Serum insulin	− 0.004	− 0.157	− 0.105
HOMA-IR	0.049	− 0.168	− 0.074
Adiponectin	0.137	− 0.038	0.038
Resistin	0.034	− 0.037	− 0.024
Total cholesterol	− 0.253*	0.161	− 0.090
HDL cholesterol	− 0.103	0.115	− 0.007
LDL cholesterol	− 0.180	0.228	0.025
Triglycerides	− 0.140	0.045	− 0.101
ASAT	0.062	− 0.085	− 0.035
ALAT	0.127	− 0.129	− 0.027
GGT	0.075	0.044	0.062
Alkaline phosphatase	− 0.377**	− 0.297*	− 0.378**
Creatinine	0.049	0.037	0.029
Calcium	0.017	0.213	0.118
Phosphorus	− 0.067	− 0.025	− 0.081
Legs fat	0.347**	− 0.115	0.105
Trunk fat	0.388***	− 0.028	0.173
Whole body fat	0.436***	− 0.126	0.150
Legs lean	0.702***	− 0.062	0.397***
Trunk lean	0.489***	− 0.336**	0.089
Whole body lean	0.640***	− 0.243*	0.253*

The results are expressed by the correlation coefficient of Pearson. Threshold of significance $p < 0.05$ (Pearson correlation test)

BMC bone mineral content, *BMI* body mass index, *HbA1c* glycated hemoglobin, *HOMA-IR* homeostasis model assessment insulin, *HDL cholesterol* high-density lipoprotein cholesterol, *LDL cholesterol* low-density lipoprotein cholesterol, *ALAT* alanine aminotransferase, *ASAT* aspartate aminotransferase, *GGT* gamma glutamyl transferases

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

association between BMI and BMD in the right femur, total hip, and the whole body. A positive correlation of BMI with legs BMC was observed, but the trunk BMC appear to be negatively associated to BMI. However, we did not find a correlation between bone markers and BMI as well as the other anthropometric parameters. Moreover, our data support that body weight is positively related with BMD and BMC, whereas waist circumference is negatively related to trunk BMC. These results are partly consistent with those of previous studies [23, 5], but our study remains the only one to invest the relation of these parameters with the BMC and the bone markers. Kim et al. have demonstrate that high body weight and BMI are positively related to high BMD and might decrease the risk of vertebral fractures, whereas waist circumference is negatively associated to BMD and might increase the risk of fractures [5]. The possible mechanism by which weight could have a positive effect on bone is that an increase in body mass accentuates mechanical loading on the skeleton, enhancing the differentiation of osteoblasts. Also, bone is an adaptative tissue that presents the capacity to modify its mass and its microarchitecture in response to mechanical stimulus [24]. Despite these significant correlations between anthropometric parameters and bone parameters, we found that only waist circumference is a significant predictor of BMD and BMC.

Table 4 Multiple linear regression analysis of association between bone mineral content (dependent variable) and the measured parameters ($n = 81$)

	Legs BMC	Trunk BMC	Whole body BMC
Age	0.224	0.167	0.215
Years since menopause	− 0.192	0.046	− 0.084
Weight	3.899	0.639	3.299
Height	− 0.595	0.841	− 0.088
Waist circumference	− 0.689**	− 0.716**	− 0.896**
BMI	− 2.108	1.171	− 0.913
Total cholesterol	− 0.095	− 0.088	− 0.054
Alkaline phosphatase	− 0.133	− 0.091	− 0.119
Legs fat	− 0.726	0.061	− 0.417
Trunk fat	− 0.644	1.366*	0.219
Whole body fat	0.546	− 2.125	− 0.951
Legs lean	0.171	0.300	0.210
Trunk lean	− 0.048	− 0.054	− 0.199
Whole body lean	− 0.120	− 0.701	− 0.229

The results are expressed by the standardized β coefficient. Threshold of significance is $p < 0.05$ (multiple linear regression test)

BMC bone mineral content, *BMI* body mass index

* $p < 0.05$; ** $p < 0.01$

In obese postmenopausal women, due to the lack of ovarian function, the dominant estrogen source becomes the fat tissue. Estrogens are steroid hormones which play a pivotal role in the maintenance of skeletal homeostasis, protecting against osteoporosis by reducing bone resorption and stimulating bone formation [25]. This mechanism can explain the positive correlation of fat mass with BMD and BMC at different skeletal sites in our population of obese postmenopausal women. Also, we have found that trunk fat was a significant predictor of BMD and this study demonstrates for the first time that trunk fat is also a predictor of trunk BMC. In other studies, fat mass has been demonstrated to have a beneficial effect, leading to an increase in bone mass [8, 26]. More recently, it was demonstrated that higher trunk fat mass was positively associated with BMD [27] and fat mass was the significant determinant of

Table 5 Correlation of bone markers with clinical and body composition parameters ($n = 81$)

	CTX-I	P1NP
Age	0.226*	0.219*
Years since menopause	0.068	0.097
Weight	− 0.062	− 0.025
Height	− 0.152	− 0.077
Waist circumference	0.020	− 0.023
BMI	0.016	0.014
Glycemia	− 0.274*	− 0.221*
HbA1c	− 0.283*	− 0.150
Serum insulin	− 0.078	− 0.098
HOMA-IR	− 0.133	− 0.151
Adiponectin	− 0.249*	− 0.255*
Resistin	0.313**	0.131
Total cholesterol	− 0.007	− 0.147
HDL cholesterol	− 0.097	− 0.121
LDL cholesterol	− 0.005	− 0.106
Triglycerides	0.001	− 0.038
ASAT	− 0.040	0.263*
ALAT	− 0.030	0.359**
GGT	− 0.014	0.340**
Alkaline phosphatase	0.511***	0.528***
Creatinine	0.090	− 0.086
Calcium	0.002	− 0.109
Phosphorus	0.170	0.125
Legs fat	0.046	0.066
Trunk fat	− 0.053	− 0.055
Whole body fat	− 0.018	0.005
Legs lean	− 0.282*	− 0.172
Trunk lean	− 0.165	− 0.065
Whole body lean	− 0.244*	− 0.121

The results are expressed by the correlation coefficient of Pearson. Threshold of significance $p < 0.05$ (Pearson correlation test)

BMI body mass index, *HbA1c* glycated hemoglobin, *HOMA-IR* homeostasis model assessment insulin, *HDL cholesterol* high-density lipoprotein cholesterol, *LDL cholesterol* low-density lipoprotein cholesterol, *ALAT* alanine aminotransferase, *ASAT* aspartate aminotransferase, *GGT* gamma glutamyl transferases, *CTX-I* C-terminal telopeptide of type I collagen, *P1NP* N-terminal propeptide of procollagen type I

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 6 Multiple linear regression analysis of association between bone markers (dependent variable) and the measured parameters ($n = 81$)

	CTX-I	P1NP
Age	− 0.056	− 0.019
Glycemia	− 0.064	0.046
HbA1c	− 0.278	0.017
Adiponectin	− 0.229*	− 0.296*
Resistin	0.280*	− 0.092
ASAT	0.129	− 0.215
ALAT	− 0.141	0.243
GGT	− 0.100	− 0.259*
Alkaline phosphatase	0.625***	0.471**
Legs lean	0.082	− 0.328
Whole body lean	− 0.155	0.373

The results are expressed by the standardized β coefficient. Threshold of significance is $p < 0.05$ (multiple linear regression test)

HbA1c glycated hemoglobin, *ASAT aspartate aminotransferase*, *ALAT* alanine aminotransferase, *GGT* gamma glutamyl transferases, *CTX-I* C-terminal telopeptide of type I collagen, *P1NP* N-terminal propeptide of procollagen type I

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

BMD at different skeletal sites [28]. However, these finding has been contradicted by other studies, showing that fat mass significantly affect BMD in postmenopausal women [29, 5]. These conflicting results suggest a complex effect of fat mass on bone tissue related to sample size, ethnicity, study design, method of statistical analysis, and population structure.

It has also been admitted that the physiological role of adipose tissue in skeletal homeostasis lies in the production of several adipokines and hormones which modulate bone remodeling via their effects on either bone formation or resorption. In vivo and in vitro studies show that adiponectin increases bone mass by activating osteoblastogenesis [30], likely indicating that a rise in adiponectin levels, caused by fat reduction, could have a beneficial effect on BMD. In accordance with this concept, we recorded that adiponectin level is inversely related to the level of bone remodeling markers and is a significant predictor of bone remodeling. Resistin, another adipokine, might also play a role in bone remodeling since it is expressed in mesenchymal stem cells, osteoblasts, and osteoclasts, and appears to increase osteoblast proliferation and osteoclast differentiation [31]. In our study, we observed a positive correlation of resistin with the bone formation and resorption markers; however, this correlation is significant only with CTX-I and linear regression analysis shows that resistin is a significant predictor of CTX-I. To our best knowledge, our finding firstly indicated that adiponectin is a significant predictor of CTX-I and P1NP and resistin is a predictor of CTX-I.

Among the parameters of the body composition, we have investigated the relationship between lean mass and bone parameters. We have found that legs, trunk, and whole body lean mass positively correlate with BMD and BMC at different skeletal sites and lean mass appears to be a significant predictor of BMD. Similarly, it has been shown that lean mass was the strongest predictor of BMD for Chinese women [32], and the main composition contributor to bone mass in Romanian women [33], and a significant contributor to femoral BMD in menopausal women [34]. The probable mechanism for this is that if an individual has a high proportion of lean mass, they have engaged in significant amount of load bearing activity, which stimulates bone growth [35].

Although several studies have explored the association between serum glucose profiles and bone metabolism, the literature is conflicting. Our finding demonstrates a positive correlation between glycemia and the whole body BMD and a negative association of bone remodeling markers with glycemia and glycated hemoglobin suggesting a probable positive effect of hyperglycemia on bone metabolism. Previously, studies reported an increase in BMD in type 2 diabetes [36, 37]. In the same context, Hyassat et al. reported that in a cohort of 1079 Jordanian postmenopausal women, type 2 diabetes was positively related to a low risk of osteoporosis [13]. Contrary to our results, Levin et al. reported a decrease in bone turnover in type 2 diabetes [38] and Arikan et al. did not find any correlation between HbA1c and BMD [39]. Probably, the heterogeneity of type 2 diabetes and the different study methodologies may be responsible for these conflicting results.

Another important result from our study is the positive correlation between P1NP and hepatic parameters (ASAT, ALAT, GGT, and Alkaline phosphatase) and CTX-I with alkaline phosphatase. Moreover, GGT and alkaline phosphatase appear to be a significant predictor of P1NP and Alkaline phosphatase, a strong predictor of CTX-I. Few studies investigating the relationship between hepatic parameters and bone have demonstrated that ALAT was inversely associated with BMD at the spine and whole body sites and bone turnover markers [40], also a negative correlation between serum GGT levels and BMD has been shown in Korean adults [41]. However, there is a lack of information about the relationship between hepatic profiles and bone parameters in postmenopausal women and further studies are needed to explain the mechanism underling these finding.

In this study, we have found that only total cholesterol was negatively related to legs BMC. However, there is no correlation of the other lipid parameters with BMD and bone markers. In this context, an epidemiological study of postmenopausal Korean women showed that level of serum total cholesterol was inversely correlated with BMD [42], but in another study, no relationship was seen between total cholesterol and BMD. Nevertheless, data about the association of lipid parameters with BMC are scarce.

This study has some limitation. The sample size was not large enough to make definite conclusion. Also, we analyzed only subjects who visited the Endocrinology Department of the National Institute of Nutrition of Tunis, for obesity or diabetes problems and may not be representative of Tunisian postmenopausal women. On the contrary, the strength of our study is that we evaluate the relationship of several biochemical parameters and body composition with bone profiles simultaneously. We also, for the first time, determined the biochemical and body composition predictor of bone mineral content and bone turnover markers.

In conclusion, we found that among the studied parameters, years since menopause, waist circumference, alkaline phosphatase, trunk fat, and lean mass are significant predictor of BMD. Moreover, waist circumference and trunk fat have significant, although contradictory, association with BMC and waist circumference appeared to be a stronger predictor than trunk fat for BMC. Also, we found that adiponectin, resistin, alkaline phosphatase, and GGT are significant predictor of bone turnover markers. Further researches are required to explore the mechanisms underlying these findings, which may have public health implications for fracture prevention strategies and the osteoporosis therapy.

Acknowledgements The authors would like to express their thanks to the patients for their participation.

Source of funding This work was funded by the "Ministry of Higher Education and Scientific Research of Tunisia."

Author contribution RC recruited patients, analyzed, interpreted data, and wrote the article; she is a guarantor. FM contributed to the recruitment of patients and the study design. HS and EC contributed to the study design and acquisition of data. MS participated in revising the article. NA contributed in the study design and following, revising the article, and giving final approval of the revision to be submitted. All authors revised the paper critically for intellectual content and approved the final version. All authors agree to be accountable for the work and to ensure that any questions relating to the accuracy and integrity of the paper are investigated and properly resolved.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Disclosures None.

References

1. Brown S, Rosen CJ (2003) Osteoporosis. Med Clin North Am 87: 1039–1063
2. Greco EA, Lenzi A, Migliaccio S (2015) The obesity of bone. Ther Adv Endocrinol Metab 6(6):273–286
3. Mazess RB, Barden HS, Ettinger M et al (1987) Spine and femur density using dual-photon absorptiometry in US white women. Bone Miner Res 2:211–219
4. Greco EA, Fornari R, Rossi F, Rossi F, Santiemma V, Prossomariti G, Annoscia C, Aversa A, Brama M, Marini M, Donini LM, Spera G, Lenzi A, Lubrano C, Migliaccio S (2010) Is obesity protective for osteoporosis? Evaluation of bone mineral density in individuals with high body mass index. Int J Clin Pract 64(6):817–820
5. Kim KC, Shin DH, Lee SY, Im JA, Lee DC (2010) Relation between obesity and bone mineral density and vertebral fractures in Korean postmenopausal women. Yonsei Med J 51(6):857–863
6. Douchi T, Kuwahata R, Matsuo T et al (2003) Relative contribution of lean and fat mass component to bone mineral density in males. J Bone Miner Metab 21:17e21

7. Wang MC, Bachrach LK, Van Loan M et al (2005) The relative contributions of lean tissue mass and fat mass to bone density in young women. Bone 37:474e481
8. Reid IR, Ames R, Evans MC et al (1992) Determinants of total body and regional bone mineral density in normal postmenopausal women a key role for fat mass. J Clin Endocrinol Metab 75:45e51
9. Reid IR, Evans MC, Ames RW (1994) Volumetric bone density of the lumbar spine is related to fat mass but not lean mass in normal postmenopausal women. Osteoporos Int 4:362e367
10. Orozco P (2004) Atherogenic lipid profile and elevated lipoprotein (a) are associated with lower bone mineral density in early postmenopausal overweight women. Eur J Epidemiol 19(12):1105–1112
11. Adami S, Braga V, Gatti D (2001) Association between bone mineral density and serum lipids in men. J Am Med Assoc 286(7):791–792
12. Suzuki K, Sugimoto C, Takizawa M, Ishizuka S, Kikuyama M, Togawa H, Taguchi Y, Nosaka K, Seino Y, Ishida H (2000) Correlations between bone mineral density and circulating bone metabolic markers in diabetic patients. Diabetes Res Clin Pract 48(3):185–191
13. Hyassat D, Alyan T, Jaddou H, Ajlouni KM (2017) Prevalence and risk factors of osteoporosis among Jordanian postmenopausal women attending the National Center for Diabetes, Endocrinology and Genetics in Jordan. BioRes Open Access 6: 85–93. https://doi.org/10.1089/biores.2016.0045
14. Farr JN, Drake MT, Amin S, Melton LJ, McCready LK, Khosla S (2014) In vivo assessment of bone quality in postmenopausal women with type 2 diabetes. J Bone Miner Res 29(4):787–795
15. Saito M, Marumo K (2010) Collagen cross-links as a determinant of bone quality: a possible explanation for bone fragility in aging, osteoporosis, and diabetes mellitus. Osteoporosis Int 21(2):195–214
16. Cherif R, Mahjoub F, Sahli H, Cheour E, Vico L, Sakly M, Attia N (2018) Positive association of obesity and insulin resistance with bone mineral density in Tunisian postmenopausal women. J Clin Densitom 21(2):163–171
17. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18(6):499–502
18. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28(7):412–419
19. Yao WJ, Wu CH, Wang ST, Chang CJ, Chiu NT, Yu CY (2001) Differential changes in regional bone mineral density in healthy Chinese: age-related and sex-dependent. Calcified Tissue Int 68(6):330–336
20. Cui R, Zhou L, Li Z, Li Q, Qi Z, Zhang J (2016) Assessment risk of osteoporosis in Chinese people: relationship among body mass index, serum lipid profiles, blood glucose, and bone mineral density. Clin Interv Aging 11:887–895
21. Szulc P, Naylor K, Hoyle NR, Eastell R, Leary ET (2017) Use of CTX-I and PINP as bone turnover markers: national bone health alliance recommendations to standardize sample handling and patient preparation to reduce pre-analytical variability. Osteoporos Int 28:2541–2556. https://doi.org/10.1007/s00198-017-4082-4
22. Lloyd JT, Alley DE, Hawkes WG, Hochberg MC, Waldstein SR, Orwig DL (2014) Body mass index is positively associated with bone mineral density in US older adults. Arch Osteoporos 9:175
23. Douchi T, Yamamoto S, Oki T, Maruta K, Kuwahata R, Yamasaki H et al (2000) Difference in the effect of adiposity on bone density between pre- and postmenopausal women. Maturitas 34:261–266
24. Frost HM (1992) The role of changes in mechanical usage set points in the pathogenesis of osteoporosis. J Bone Miner Res 7:253–261
25. Reid I (2002) Relationships among body mass, its components, and bone. Bone 31:547–555
26. Khosla S, Atkinson EJ, Riggs BL, Melton LJ (1996) Relationship between body composition and bone mass in women. J Bone Miner Res 11:857–863
27. Saarelainen J, Honkanen R, Kröger H, Tuppurainen M, Jurvelin JS, Niskanen L (2011) Body fat distribution is associated with lumbar spine bone density independently of body weight in postmenopausal women. Maturitas 69(1):86–90
28. Nur H, Toraman NF, Arica Z, Sarier N, Samur A (2013) The relationship between body composition and bone mineral density in postmenopausal Turkish women. Rheumatol Int 33(3):607–612
29. Liu S, Li J, Sheng Z, Wu X, Liao E (2011) Relationship between body composition and age, menopause and its effects on bone mineral density at segmental regions in Central Southern Chinese postmenopausal elderly women with and without osteoporosis. Arch Gerontol Geriatr 53:192–197
30. Jurimae J, Rembel K, Jurimae T, Rehand M (2005) Adiponectin is associated with bone mineral density in perimenopausal women. Horm Metab Res 37:297–302
31. Thommesen L, Stunes A, Monjo M, Grosvik K, Tamburstuen M, Kjobli E et al (2006) Expression and regulation of resistin in osteoblasts and osteoclasts indicate a role in bone metabolism. J Cell Biochem 99:824–834
32. Cheng Q, Zhu YX, Zhang MX, Li LH, Du PY, Zhu MH (2012) Age and sex effects on the association between body composition and bone mineral density in healthy Chinese men and women. Menopause 19:448–455
33. Georgescu CE, Ilie I, Brad C, Duncea I (2010) Association between body composition and bone mineral density in healthy, non-obese, young Romanian adults and effects of menopause. Maedica (Buchar) 5:24–27
34. Li S, Wagner R, Holm K, Lehotsky J, Zinaman MJ (2006) Relationship between soft tissue body composition and bone mass in perimenopausal women. Maturitas 117:1462–1470
35. Weeks BK, Beck BR (2008) The BPAQ: a bone-specific physical activity assessment instrument. Osteoporos Int 19(11):1567–1577
36. Thrailkill KM, Lumpkin CK, Bunn RC, Kemp SF, Fowlkes JL (2005) Is insulin an anabolic agent in bone? Dissecting the diabetic bone for clues. Am J Physiol Endocrinol Metab 289(5):E735–E745
37. Van Daele PL, Stolk RP, Burger H et al (1995) Bone density in non-insulin-dependent diabetes mellitus. The Rotterdam Study. Ann Intern Med 122:409e414
38. Levin ME, Boisseau VC, Avioli LV (1976) Effects of diabetes mellitus on bone mass in juvenile and adult-onset diabetes. N Engl J Med 294:241e245
39. Arikan S, Tuzcu A, Bahceci M, Ozmen S, Gokalp D (2012) Insulin resistance in type 2 diabetes mellitus may be related to bone mineral density. J Clin Densitom 15(2):186–190
40. Xia MF, Lin HD, Yan HM, Bian H, Chang XX, Zhang LS, He WY, Gao X (2016) The association of liver fat content and serum alanine aminotransferase with bone mineral density in middle-aged and elderly Chinese men and postmenopausal women. J Transl Med 14(11):11
41. Choi HS, Kim KJ, Rhee Y, Lim SK (2015) Serum γ-glutamyl transferase is inversely associated with bone mineral density independently of alcohol consumption. Endocrinol Metab 31:64–71
42. Cui LH, Shin MH, Chung EK, Lee YH, Kweon SS, Park KS, Choi JS (2005) Association between bone mineral densities and serum lipid profiles of pre- and post-menopausal rural women in South Korea. Osteoporosis Int 16(12):1975–1981