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ORIGINAL CONTRIBUTIONS

Alterations in Fat Mass and Bone Mineral Density Are Associated with Decreased Lipocalin-2 After Laparoscopic Sleeve Gastrectomy in Obese Chinese Women

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Abstract

Objective Lipocalin-2 (LCN2) plays an important role in the regulation of the obesity and obesity-related dysmetabolic state. This study aimed to analyze serum LCN2 level in Chinese women with obesity before and after laparoscopic sleeve gastrectomy (LSG) and determine the association between alteration in fat mass and bone mineral density (BMD) and LCN2 level.

Methods Fifty-two women (38 patients with obesity and 14 with normal body mass index (BMI)) were enrolled in this study. All patients with obesity underwent LSG. BMDs of the arm, leg, thoracic and lumbar spine, and pelvis were measured by dual-energy X-ray absorptiometry. Body fat mass and distribution were measured by dual-energy X-ray absorptiometry, and routine anthropometric/laboratory biochemical parameters at baseline and 3 and 12 months after LSG were recorded. Serum LCN2 levels were measured using an enzyme-linked immunosorbent assay.

Results Serum LCN2 level was significantly higher in women with obesity than in the controls with normal BMI (102.70 ± 27.19 vs. 80.66 ± 19.55 ng/mL, $P = 0.009$). LCN2 level was decreased at 3 and 12 months after LSG (86.73 ± 26.79 ng/mL, $P = 0.171$, and 64.79 ± 28.39 ng/mL, $P < 0.001$, respectively). LSG led to marked body fat mass and slight BMD decrease. Decreased LCN2 level was significantly correlated with alterations in left and right leg BMDs and trunk fat mass at 12 months after LSG.

Conclusions Obesity was associated with up-regulated serum LCN2 level. Decreased LCN2 level was positively correlated with changes in BMD and fat mass at 12 months after LSG in Chinese women.

Keywords Lipocalin-2 · Bone mineral density · Body fat distribution · Obesity · Laparoscopic sleeve gastrectomy

Introduction

Bariatric surgery has gained much attention due to the increased prevalence of obesity. Recently, several studies reported that bariatric surgery can markedly decrease body fat distribution [1, 2]. Besides, bariatric surgery has been proven to have an effect on bone metabolism. For instance, cortical and trabecular volumetric bone mineral density (BMD) gradually reduced over 24 months after Roux-en-Y gastric bypass surgery [3]. BMD gradually decreased in Chinese women with obesity after laparoscopic sleeve gastrectomy (LSG) [4].

Lipocalin-2 (LCN2), also known as neutrophil gelatinase-associated lipocalin (NAGL), is a member of the lipocalin superfamily [5]. LCN2 is a secreted glycoprotein that was previously considered an adipokine. However, Mosialou et al. reported that LCN2 is expressed at an at least tenfold higher concentration in the bone than in fat or any other tissue [6]. Although controversial, several studies have suggested

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that LCN2 plays an important role in obesity [7, 8]. A 60% increase in serum LCN2 levels was observed in individuals with obesity compared with that in individuals with normal body mass index (BMI) [9]. Although there was no difference in serum LCN2 level between the two groups in another study, a significant upregulation of LCN2 expression in the visceral adipose tissue was reported in the study [10]. Moreover, few studies have described the effect of LSG on LCN2 levels.

Thus, the current study aimed to determine the serum LCN2 levels in Chinese women with obesity and evaluate the changes in LCN2 levels after LSG. Furthermore, we aimed to confirm whether these changes are correlated with changes in body fat distribution and BMD.

Methods

Patients

This retrospective study included 38 women with obesity that underwent LSG from Shanghai Tenth People's Hospital, between July 2016 and July 2017. Patients returned to the hospital at 3 and 12 months after surgery and underwent a comprehensive medical examination which are described below. The inclusion criteria were BMI > 35 kg/m^2, or BMI > 30 kg/m^2 with two or more obesity-related comorbidities, such as type 2 diabetes mellitus, hypertriglyceridemia, hypertension, or non-alcoholic fatty liver but otherwise healthy status [11]. As Fig. 1 showed, subjects were excluded from the study if one of the following criteria is present: (1) presence of severe cardiac, hepatic, or renal failure; (2) presence of severe systemic diseases (cancer or autoimmune diseases); (3) use of medications (vitamin D, calcium and derivatives, steroid hormones, antidepressants, and sex hormones) that affect body weight or bone metabolism; (4) presence of endocrine diseases causing obesity; (5) lactation or pregnancy; and (6) unwilling to continue follow-up study [12–17]. Fourteen healthy women with normal BMI (WHO recommended international standard: BMI range 18.5 from 25) and age matched were from the medical examination center in the same period. The exclusion criteria were as follows:(1) clinical or laboratory evidence indicates that the heart, liver, and kidney function are seriously impaired; (2) serious systemic diseases such as various malignant tumors, autoimmune diseases, systemic allergic diseases, and acute and chronic inflammation; (3) lactation or pregnancy; (4) age, sex, BMI, or laboratory data missing. Informed consent was obtained from all individual participants included in this study.

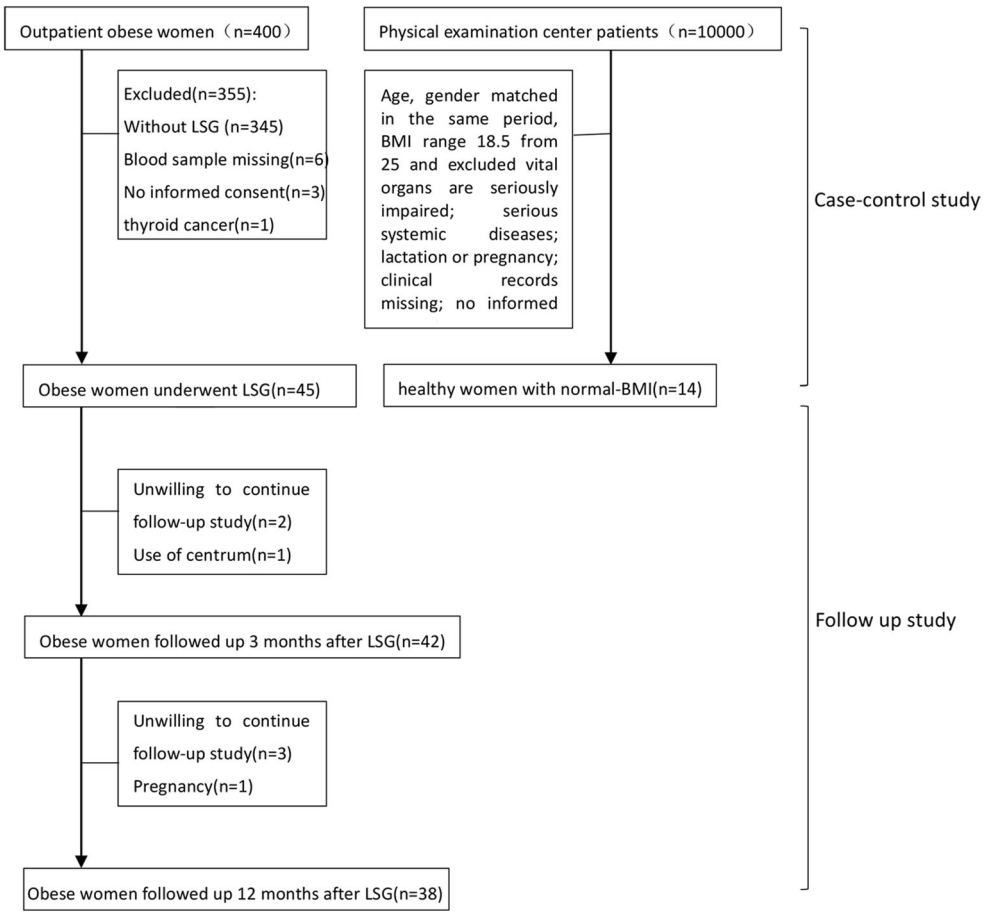

Fig. 1 Study flow chart

Measurement of Anthropometric Data

The BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), and levels of fasting blood glucose (FBG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and uric acid (UA) were measured.

Measurement of BMD and Bone Metabolic Markers

BMD of the arm, leg, thoracic and lumbar spine, and pelvis was measured by dual-energy X-ray absorptiometry. The levels of bone metabolic markers, including calcium, intact parathyroid hormone (iPTH), 25-hydroxy vitamin D (25(OH)VitD), type I collagen carboxy-terminal peptide (CTX), and osteocalcin (OC), were measured.

Measurement of Body Fat Mass and Fat Distribution

Body fat mass and fat distribution in the whole body, trunk, and limb were measured with high accuracy by dual-energy X-ray absorptiometry (DXA) (Hologic QDR 4500, USA) at baseline and 3 and 12 months after the LSG.

Serum LCN2 Assay

Serum LCN2 levels were measured by Quantikine human LCN2 enzyme-linked immunosorbent assay kit (R&D Systems; Catalog Number DLCN20).

Statistical Analysis

All data were analyzed using SPSS software version 20.0. Data were presented as means ± standard deviation (SD) for continuous distribution and median ± interquartile range for skewed distribution. Independent sample *t* test was performed to compare the variables between women with obesity and normal BMI. Dunnett *t* tests were used to compare the variables between baseline and 3 and 12 months after LSG. Pearson's correlation analysis was used to investigate the association between two indices. Linear regression analysis was performed to analyze the relationship between the changes in body fat distribution and BMD and changes in LCN2 levels. Results with *P* value < 0.05 were considered to be statistically significant.

Results

Clinical Characteristics of the Subjects

Basic anthropometric examination data and biochemical indices are summarized in Table 1. The mean ± SD BMI in women with normal weight was 21.77 ± 1.12 kg/m^2 (range, 20.56–22.89 kg/m^2) and that in women with obesity was 38.81 ± 5.51 kg/m^2 (range, 33.3–44.32 kg/m^2). LCN2 levels in the obesity group were higher than in the normal group (102.70 ± 27.19 vs. 80.66 ± 19.55 ng/mL, $P = 0.009$), as shown in Fig. 2a. Compared to women with normal weight, women with obesity had higher SBP, DBP and FBG, ALT, AST, TG, UA levels (for all, $P < 0.05$) and lower Cr and HDL levels.

Change in Serum LCN2 Levels After LSG

In women with obesity, LCN2 levels decreased at 3 months after LSG (86.73 ± 26.79 ng/mL, $P = 0.171$, but this trend did not reach statistical significance. Meanwhile, the decreased trend from baseline to 12 months of follow-up has reached a level of statistical significance (64.79 ± 28.39 ng/mL, $P < 0.001$). All data are shown in Fig. 2b.

Body Fat Mass and Distribution After LSG

The regional distribution of changes in fat mass resulting from LSG was analyzed (Fig. 3a). There was a marked reduction in total and regional body fat mass from baseline to 3 and 12 months of follow-up (all $P < 0.001$). Besides, the trunk region accounted for more fat loss than the limbs.

Table 1 Clinical and biochemical characteristics of the patients

Characteristics	Normal weight ($n = 14$)	Obesity ($n = 38$)	*P* value
Age (years)	32.64 ± 11.64	31.18 ± 10.03	0.658
Weight (kg)	64.64 ± 5.47	106.12 ± 16.88	< 0.001***
BMI (kg/m^2)	21.77 ± 1.12	38.81 ± 5.51	< 0.001***
SBP (mmHg)	109.29 ± 12.41	135.11 ± 20.71	< 0.001***
DBP (mmHg)	71.86 ± 7.0	82.05 ± 14.21	0.013*
FBG (mmol/L)	4.89 ± 0.39	6.76 ± 2.94	< 0.001***
ALT (U/L)	22.36 ± 20.27	46.01 ± 37.55	0.031*
AST (U/L)	22.07 ± 5.25	31.60 ± 22.64	0.019*
Cr (μmol/L)	77.43 ± 10.54	59.34 ± 14.84	< 0.001***
TC (mmol/L)	4.64 ± 0.72	4.75 ± 1.23	0.697
TG (mmol/L)	1.15 ± 0.49	2.27 ± 1.85	0.001**
HDL (mmol/L)	1.36 ± 0.32	1.02 ± 0.24	< 0.001***
LDL (mmol/L)	2.97 ± 0.68	2.78 ± 0.96	0.511
UA (μmol/L)	342.00 ± 61.91	403.29 ± 102.09	0.041*
LCN2 (ng/mL)	80.66 ± 19.55	102.70 ± 27.19	0.009**

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FBG* fasting blood glucose, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *Cr* creatinine, *TC* serum total cholesterol, *TG* triglyceride, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *UA* uric acid, *LCN2* lipocalin-2

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

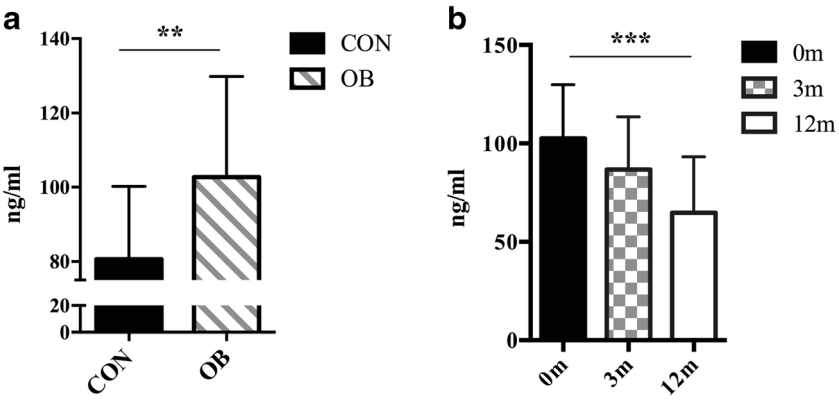

Fig. 2 Serum LCN2 levels. **a** The LCN2 level between women with obesity and women with normal weight. **b** Change in LCN2 levels at 3 and 12 months after LSG. Comparison of variables at 3 and 12 months after LSG and baseline, $^{**}P < 0.01$, $^{***}P < 0.001$

BMD and Bone Metabolic Markers After LSG

As shown in Fig. 3b, total and regional BMD decreased at 3 and 12 months after LSG, but this trend did not reach statistical significance. The levels of OC related to bone formation and type I collagen CTX related to bone resumption increased at 3 and 12 months after LSG ($P < 0.05$). Furthermore, OC/CTX level significantly decreased at 3 and 12 months compared to those at baseline (Fig. 4a). Meanwhile, there was no significant change in calcium, 25(OH)VitD, and iPTH levels after surgery (Fig. 4b).

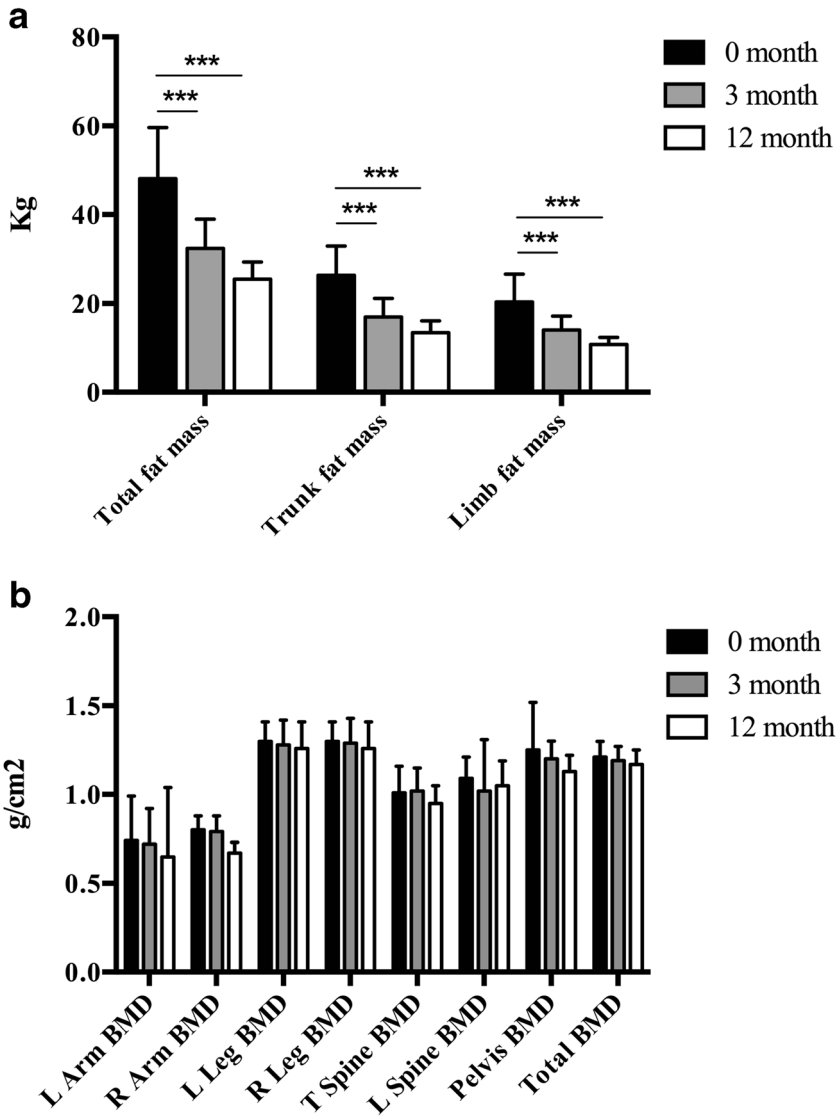

Fig. 3 **a** Body fat distribution (total, trunk, and limb) at baseline and 3 and 12 months after LSG. There was a significant reduction in total and regional fat mass. $^{***}P < 0.001$. **b** Changes in total and regional (left and right arms, left and right legs, thoracic and lumbar spine, pelvis) BMDs at 3 and 12 months after LSG

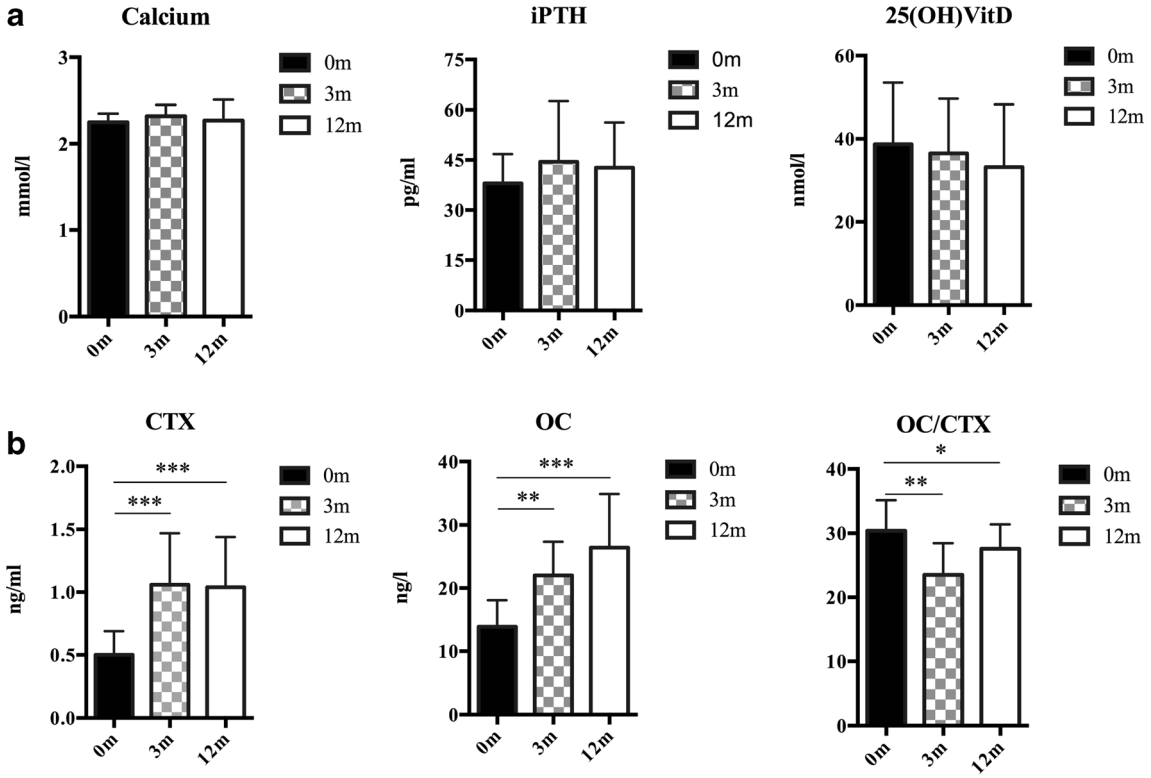

Fig. 4 **a** Changes in OC, CTX, and OC/CTX at 3 and 12 months after LSG. Comparison of variables at 3 and 12 months after LSG and baseline. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. **b** Change in calcium, 25(OH)VitD, and iPTH levels at 3 and 12 months after LSG. Comparison of variables at 3 and 12 months after LSG and baseline

Change in Serum LCN2 Level Is Related to Body Fat Distribution and BMD After LSG

To further explore the association between decreased LCN2 level and decreased body fat distribution/BMD, single-factor correlation was performed. As shown in Table 2, decreased LCN2 level was significantly associated with change in the left and right leg BMD and trunk fat mass at 12 months after LSG ($r = 0.842$, $P = 0.035$; $r = 0.857$, $P = 0.014$; $r = 0.663$, $P = 0.036$). To evaluate the contribution of BMD and body fat distribution towards serum LCN2 levels, a linear regression analysis was performed (Table 3). The changes in the left and right leg BMD and trunk fat mass were significantly correlated with changes in LCN2 levels. After adjusting the age, BMI, and trunk fat mass, the changes in the BMD were also significantly correlated with LCN2 levels variation.

Discussion

LCN2 was initially discovered to be involved in the innate immune response to bacterial infection, as well as regulation of cell proliferation and apoptosis [18]. Recently, it was found that this protein may play a pivotal role in obesity and obesity-related dysmetabolic state [7–10]. The current study focuses on the following three questions: 1. Compared to controls with normal BMI, is serum LCN2 level significantly increased in Chinese women with obesity? 2. Is serum LCN2 level gradually changed in women with obesity after LSG? 3. If it is so, is the change in BMD and fat mass correlated with changes in LCN2 levels?

Table 2 Associations between change in LCN2 level and BMD and changes in body fat distribution after LSG

	ΔLCN2-3		ΔLCN2-12	
	r	*P* value	*r*	*P* value
ΔL arm BMD	0.183	0.637	0.496	0.211
ΔR arm BMD	0.310	0.417	0.212	0.649
ΔL leg BMD	0.005	0.989	0.842	0.035*
ΔR leg BMD	0.590	0.095	0.857	0.014*
ΔT spine BMD	0.587	0.096	0.126	0.788
ΔL spine BMD	0.397	0.291	0.245	0.596
ΔPelvis BMD	0.585	0.098	0.175	0.707
ΔTotal BMD	0.540	0.908	0.432	0.285
ΔTrunk fat mass	0.108	0.753	0.663	0.036*
ΔLimb fat mass	0.365	0.270	0.243	0.499
ΔTotal fat mass	0.367	0.367	0.465	0.175

ΔLCN2-3 means comparison of LCN2 at 3 months after LSG and baseline. ΔLCN2-12 means comparison of LCN2 at 12 months after LSG and baseline

$^{*}P < 0.05$

Table 3 Multiple linear analysis of the relationship between change in LCN2 level and BMD changes at 12 month after LSG

Model	ΔLCN2		
	β	R^2	P value
1	0.943	0.867	0.001**
2	0.826	0.887	0.016*
3	0.635	0.992	0.031*

Model 1: ΔR leg BMD. Model 2: ΔR leg BMD, adjusting age and ΔBMI. Model 3: ΔR leg BMD, adjusting age, ΔBMI, and ΔTrunk fat mass

*$P < 0.05$; **$P < 0.01$

LCN2, also known as NAGL, is a 25-kDa glycoprotein originally purified from human neutrophils. It belongs to the lipocalin superfamily, which can bind and transport small lipophilic molecules. LCN2 is expressed in many tissues, including those in fats, kidneys, liver, lungs, bones, thymus, and small intestine. Jang et al. provided the first evidence demonstrating that serum LCN2 levels are closely associated with obesity [19]. Other studies also confirmed that patients with metabolic syndrome (MetS) have higher LCN2 levels than those without MetS. A study of 229 individuals with obesity reported positive correlations between the serum LCN2 levels and adiposity, hypertriglyceridemia, hyperglycemia, and high-sensitivity CRP levels [6]. Serum LCN2 levels are also correlated with obesity and BMI, especially in severely obese women [20]. Many studies indicated that the expression of LCN2 is controlled by inflammation and metabolic state. Moreover, various inflammatory factors (TNFα, IL1β, and IL6), nutrients (palmitate, and oleate), and insulin induce LCN2 expression, mainly in a NFkB-dependent manner [21]. STAT1 binding sites in the LCN2 promoter mediates IFNγ induction of LCN2 expression [22]. However, a few studies reported contradictory conclusions. They observed no differences in plasma LCN2 levels, rather than increased circulating LCN2/matrix metallopeptidase 9 (MMP-9) complex levels [10]. LCN2 modulates MMP-9 (regulates the balance between synthesis and degradation of matrix proteins) activity by protecting it from degradation, implying that it may be indirectly involved in the obesity development [23]. Our study confirmed that LCN2 level was higher in Chinese women with obesity than in women with normal BMI, which was consistent with the results of most previous studies.

Bariatric surgery has proven to be effective in weight loss, reducing fat mass and improving glucose and lipid metabolism [24]. Our results supported the aforementioned viewpoints. There was marked reduction in total and regional body fat mass (especially trunk fat mass) between baseline and at the 3- and 12-month of follow-up in women with obesity. However, the effect of LSG on LCN2 levels was not investigated in the previous study. Furthermore, we noted that the serum LCN2 levels gradually decreased in women with obesity after LSG, whether in the short or long term.

LCN2, previously considered an adipokine, is expressed at an at least tenfold higher concentration in the bone than in fat or any other tissue recently [5]. Is change in BMD and fat mass correlated with changes in LCN2 levels? Bariatric surgery has potential adverse effects on bone metabolism including the risk of fractures [25]. In this study, although the P value does not demonstrate a statistically significant difference, there was a trend of bone loss in women with obesity after LSG. Lack of nutrient absorption leads to insufficient bone raw materials, which may be the underlying reasons for the above phenomenon [26]. However, this study did not find significant change in calcium, 25(OH)VitD, and iPTH levels after surgery. Increased OC and CTX after LSG indicated active osseous metabolism. Costa et al. found that LCN2 is involved in bone development and turnover. It also has a negative effect on bone formation, affecting growth plate development and interfering with osteoblast differentiation [27]. Lim et al. have demonstrated that circulating LCN2 levels predict future risk of osteoporotic fracture [28]. LCN2 may be a novel mechanoresponsive gene that could be central to the pathological response in the long bones [29]. Moreover, several earlier reports have revealed the relationship between LCN2 and adipose tissue. Studies suggested that LCN2 mRNA and protein expression was substantially increased in the visceral adipose tissue and positively correlated with inflammatory markers [18].

To further validate our conjecture, single-factor correlation and multiple-factor regression analysis were performed. It showed that changes in left and right leg BMDs and trunk fat mass were significantly correlated with changes in LCN2 levels at 12 months after LSG. Moreover, compared to body fat distribution, BMD contributes more to serum LCN2 level. We assumed this may be because the bone is the main LCN2-secreting tissue.

It should be noted that there are few limitations with this current study. First, because this is an observational study, causality cannot be assumed. Second, the follow-up period was relatively short, and the sample size was small. Additionally, because the cohort included only Chinese women, any findings may not be generalizable to men or even other ethnic groups. Thirdly, we cannot exclude the effect of any unmeasured bias or confounding factors; therefore, these findings should be interpreted cautiously until the findings are replicated in other studies. Finally, BMD measured by DEXA may be affected by soft tissue, etc.

Conclusion

In this study, serum LCN2 levels were higher in women with obesity than in women with normal BMI and gradually decreased after LSG. Decreased LCN2 levels were significantly correlated with change in BMD and fat mass at 12 months after LSG.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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

Ethical Approval The study was approved by the ethics committee of Shanghai Tenth People's Hospital.

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