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ORIGINAL ARTICLE

Bone metabolism markers are associated with neck circumference in adult Arab women

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Abstract

Summary The study aimed to determine whether neck circumference is associated with bone metabolism markers among adult Arab women and found modest but significant associations with bone resorption markers, suggesting that neck circumference, a surrogate measure of upper subcutaneous fat, influences bone turnover expression among adult females.

Introduction Body fat distribution is associated with decreased bone resorption and neck circumference (NC), a surrogate measure for upper body fat, has never been tested as a marker that can reflect bone turnover. This is the first study aimed to analyze the associations between NC and several bone biomarkers among adult Saudi women.

Methods This cross-sectional study included a total of 265 middle-aged Saudi women [86 non-obese (mean age 52.7 ± 8.1; mean BMI 26.9 ± 2.3) and 179 obese (mean age 50.6 ± 7.5; mean BMI 35.7 ± 4.5)] recruited from primary care centers in Riyadh, Saudi Arabia. Anthropometrics included BMI, NC, waist and hip circumferences, total body fat percentage (%), and blood pressure. Biochemical parameters included glucose and lipid profile which were measured routinely. Serum levels of 25(OH) D, parathyroid hormone, RANKl, sclerostin, C-terminal telopeptide of collagen I (CTX-I), Dkk1, IL1β, osteoprotegerin, osteopontin, and osteocalcin were measured using commercially available assays.

Results In all groups, NC was inversely associated with PTH ($R = -0.22$; $p < 0.05$) and positively associated with osteoprotegerin ($R = 0.20$; $p < 0.05$) even after adjustments for age and BMI. Using all anthropometric indices as independent variables showed that only NC explained the variance perceived in CTX-I ($p = 0.049$). In the non-obese, waist-hip ratio (WHR) was significantly associated with sclerostin ($R = 0.40$; $p < 0.05$) and body fat was significantly associated with osteopontin ($R = 0.42$; $p < 0.05$).

Conclusion NC is modestly but significantly associated with bone biomarkers, particularly the bone resorption markers, among adult Arab women. The present findings highlight the importance of NC as measure of upper body subcutaneous fat in influencing bone biomarker expression in adult females.

Keywords Bone turnover markers · Neck · Obesity · Women

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Introduction

Obesity in general is a well-known cause of chronic metabolic abnormalities, and the risk of obesity-related diseases varies depending on where the excess adipose tissue is distributed in the body [1]. Emerging evidence has also linked excess fat to bone-related diseases such as osteoporosis [2]. Both adipose and bone tissue come from the same progenitor mesenchymal cells and both act as endocrine organs capable of producing hormones, providing a solid foundation to investigate the mechanisms behind this intricate association [2]. While the existence of an association seems clear, the confusion stems from obesity acting both as a protective state and a risk factor for osteoporosis [3]. The most current evidence indicate that increased weight or body mass index (BMI) translates to higher bone mineral density (BMD) but the parallel increase in adiposity alters bone-regulating hormones that can diminish bone quality [4]. It seems plausible to investigate that body fat and its distribution may offer insights as to which among these indices are beneficial or detrimental to bone health. Lower body fat mass in general was observed to be an independent risk factor for higher bone loss at the lumbar spine in women, not men [5]. Furthermore, the recent study of Wang and colleagues involving more than 5000 Chinese adults observed that while, BMI, fat, and lean masses were positively correlated with BMD in both sexes, subcutaneous fat was inversely associated with BMD and positively associated with osteocalcin only in post-menopausal females [6]. In these previous studies, the metabolic effects of body fat in bone health were highlighted, but not all anthropometric indices were included. Among the understudied anthropometric measure is the upper body fat distribution, particularly neck skinfold [7] and neck circumference (NC) [8, 9] which have also been used as an index for adverse risk profile [10], but not in terms of bone health. To the best of our knowledge, NC, as compared to more conventional measures of obesity such as BMI and waist circumference, has never been investigated for its possible associations with bone biomarkers. The present study aims to fill this gap.

Methods

The present cross-sectional study is a sub-cohort analysis of a larger study on the associations of neck circumference and cardiometabolic risk conducted in King Khalid University Hospital and primary health care centers in collaboration with Biomarkers Research Program in King Saud University (KSU) in Riyadh, Kingdom of Saudi Arabia (KSA), from September 2014 to April 2016, using a total of 623 Saudi women aged 18–70 years (data on file). For the purpose of this study, 265 participants aged 35–70 years were randomly selected in the database of the larger study. They were subdivided according to obese (BMI ≥ 30 kg/m^2) and non-obese (BMI < 30 kg/m^2). Written informed consent was obtained from each participant prior to inclusion. Ethical approval was obtained from the Ethics Committee of the College of Science in KSU, Riyadh, KSA.

Anthropometrics

All anthropometric measurements were taken by a team of well-trained health care providers using standardized procedures and equipment. The height was recorded to the nearest 0.5 cm. The weight was recorded to the nearest 0.1 kg, taken without shoes and with light clothing. BMI was calculated as weight (kg)/height (m^2). Waist and hip circumferences were measured to the nearest 0.1 cm using standardized tape measure. Waist-to-hip ratio (WHR) was calculated by dividing the waist circumference (cm) and hip circumference (cm). NC was measured to the nearest 0.1 cm, with the tape measure placed horizontally at the midway of the neck between mid-cervical spine and mid-anterior neck, just below the laryngeal prominence. Systolic and diastolic blood pressure was measured using digital sphygmomanometer. Total body fat percentage (%) as well as android and gynoid fat (%) were assessed using a dual-energy X-ray absorptiometry (DXA) device (Prodigy Advance, GE healthcare, Madison, WI, USA).

Biochemical parameters

An overnight fasting (10–12 h) serum sample was collected in all participants. Samples were analyzed and stored in the BRP, College of Science, KSU. In brief, all blood and serum samples were placed in plain polystyrene tubes, delivered on the same day to BRP and stored at − 20 °C. Fasting blood glucose and lipid profile were measured using a standard chemical analyzer (Konelab, Vantaa, Finland).

Serum 25(OH)D and bone markers

Circulating levels of serum 25(OH) D and C-terminal telopeptide of collagen I (CTX-I) were measured using electrochemiluminescence (ECL) immunoassay on Roche Elecsys Cobas e411 analyzer (Roche Diagnostics, GmbH, Mannheim, Germany). Dkk-1 (Dickkopf-1), OPG (osteoprotegerin), OC (osteocalcin), OPN (osteopontin), SOST (Sclerostin), IL-1β, and PTH (parathyroid hormone) were measured using the Milliplex MAP Human Bone Magnetic Bead Panel (HBNMAG-51K). RANKL was done by the MILLIPLEX MAP Human RANKL Magnetic Bead-Single

Plex (HRNKLMAG-51 K-01). The intra- and inter-assay CVs are < 10% and < 15% respectively.

Statistical analysis

Statistical analyses were performed using SPSS 22 (IBM Corp., Armonk, NY, USA). Continuous data were presented as mean ± standard deviation (SD) and median (25th–75th) percentiles for variables following normal and non-normal variables, respectively. Continuous variables were checked for normality using graphs, Kolmogorov-Smirnov test, as well as skewness and kurtoses (≤ 0.8). Non-normal continuous variables were transformed to log or SQRT where appropriate. Neck circumference, WC, BMI, and total body fat percentage were standardized to facilitate comparisons of coefficients. Regression analysis was done to determine associations of NC to parameters assessed using age and menopausal status as covariates. All tests were two-sided and statistical significance was set at p value < 0.05.

Results

Table 1 shows the general characteristics of all participants. A total of 265 participants [86 non-obese (mean age 52.7 ± 8.1; mean BMI 26.9 ± 2.3) and 179 obese (mean age 50.6 ± 7.5; mean BMI 35.7 ± 4.5)] were included in this cross-sectional study. There was no significant difference in the prevalence of menopause in the non-obese (45.3%) and the obese (41.3%). Non-obese participants were significantly older ($p = 0.04$) than obese. As expected, obese participants had significantly higher NC and total body fat (%) than non-obese (p values < 0.001) as well as significantly higher systolic blood pressure than non-obese ($p = 0.02$). No other significant differences were noted in

Table 1 Clinical characteristics of participants according to obesity status

Parameters	Non-obese	Obese	Unadjusted p value	Adjusted p value
N	86	179		
Menopause (%)	39 (45.3)	75 (41.9)	0.48	
Age (years)	52.7 ± 8.1	50.6 ± 7.5	*0.04*	
BMI (kg/m^2)	26.9 ± 2.3	35.7 ± 4.5	*< 0.001*	*< 0.001*
NC (cm)	35.1 ± 2.4	37.1 ± 2.2	*< 0.001*	*< 0.001*
WHR	0.91 ± 0.1	0.91 ± 0.8	0.65	0.97
Total body fat (%)	42.3 ± 4.1	48.6 ± 3.5	*< 0.001*	*< 0.001*
Android body fat (%)	44.8 ± 5.9	51.4 ± 4.5	*< 0.001*	*< 0.001*
Gynoid body fat (%)	44.6 ± 7.5	49.5 ± 3.2	*< 0.001*	*< 0.001*
Systolic blood pressure (mmHg)	120.5 ± 15.7	126.1 ± 18.5	*0.02*	*0.005*
Diastolic blood pressure (mmHg)	72.6 ± 10.5	75.3 ± 11.1	0.07	0.06
Glucose (mmol/l)#	7.1 ± 3.3	7.3 ± 2.9	0.59	0.56
Total cholesterol (mmol/l)	5.0 ± 1.01	5.1 ± 0.9	0.69	0.78
HDL-cholesterol (mmol/l)	1.3 ± 0.3	1.2 ± 0.3	0.07	0.058
LDL-cholesterol (mmol/l)	3.1 ± 1.06	3.1 ± 0.9	0.94	0.79
Triglycerides (mmol/l)#	1.4 (1.1–1.9)	1.5 (1.2–2.1)	0.12	0.39
25(OH)D (nmol/l)#	81.7 (49–106)	71.6 (45–101)	0.17	0.26
Rankl (pg/ml)#	35.4 (23–54)	32.0 (22–58)	0.47	0.53
SOST (ng/ml)	2.1 (1.3–3.4)	2.1 (1.4–3.0)	0.75	0.79
CTX-I (pg/ml)#	40.0 (10.0–70.8)	20.0 (10.0–70.0)	0.54	0.61
PTH (pg/ml)#	16.2 (14–25)	17.4 (10–26)	0.59	0.32
Dkk1 (μg/ml)	3.1 ± 1.4	3.0 ± 1.1	0.80	0.50
IL1β (pg/ml)#	0.57 (0.2–2.7)	0.36 (0.2–2.0)	0.15	0.52
OPG (ng/ml)	0.63 ± 0.24	0.72 ± 0.26	0.14	0.16
OPN (ng/ml)	3.4 (0.99–6.3)	3.2 (1.7–5.2)	0.89	0.46
OC (ng/ml)	8.5 ± 6.3	8.5 ± 5.7	0.98	0.94
PINP (ng/ml)	17.9 (8.5–33.6)	16.4 (5.9–24.8)	0.26	0.28

The number sign denotes non-normal variable and is presented as median; data presented as mean ± SD for normal variables while median (quartile 1–quartile 3) for non-normal variables; covariates include age and menopausal status; p values < 0.05 are considered significant and in italics; the italics are only to emphasize that the entries were significant (< 0.05)

glucose and lipid profile as well as other parameters, even after adjusting for age and menopausal status (Table 1).

Table 2 shows the associations between NC and adiposity indices as well as clinical and bone biomarker parameters after adjustments for age and menopausal status. In all participants, NC was significantly associated with most adiposity indices with the exception of gynoid body fat %. NC was also significantly associated with glucose ($R = 0.30$; $p < 0.01$) and triglycerides ($R = 0.32$; $p < 0.01$) (Table 2). NC was inversely associated with 25(OH) D ($R = -0.17$; $p < 0.05$) and PTH ($R = -0.22$; $p < 0.05$) as well as a positive and significant association with OPG ($R = 0.20$; $p < 0.05$). As to the association of other adiposity indices, BMI was inversely associated with Dkk1 ($R = -0.22$; $p < 0.05$). WHR on the other hand was positively associated with RANKl ($R = 0.19$; $p < 0.05$) and Dkk1 ($R = 0.32$; $p < 0.01$) and inversely associated with IL1β ($R = -0.25$; $p < 0.05$). Stratification according to obesity status revealed no associations of BMI to bone biomarkers in the non-obese group. Nevertheless, also in the non-obese, WHR was significantly and inversely associated with PTH ($R = -0.50$; $p < 0.05$) and body fat was significantly associated with OPN ($R = 0.45$; $p < 0.05$). Among obese participants, NC was inversely associated with PTH ($R = -0.37$; $p < 0.01$) and BMI is inversely associated with OPG ($R = -0.29$; $p < 0.05$). Lastly, WHR in the obese group was significantly associated with Dkk1 ($R = 0.30$; $p < 0.05$). Total body fat percentage was not associated with any bone biomarkers in the obese group. The rest of the associations are presented in Table 2.

Table 3 shows the differences between the variables measured according to menopausal status [pre-menopausal $N = 151$ (age 48.2 ± 6.9; BMI 33.1 ± 5.7); post-menopausal $N = 114$ (age 55.4 ± 6.8; BMI 32.5 ± 5.7)] adjusted for age and matched for BMI. NC was significantly higher in the pre-menopausal group than the post-menopausal group ($p = 0.003$). Consequently, IL1β was also significantly higher in the pre-menopausal as compared to the post-menopausal group ($p = 0.04$). The rest of the differences were not significant (Table 3).

Table 2 Associations of NC with other parameters in normal and obese participants

Parameters	All ($N = 265$)				Non-obese ($N = 86$)				Obese ($N = 179$)			
	NC	BMI	WHR	BF	NC	BMI	WHR	BF	NC	BMI	WHR	BF
NC (cm)	1				1				1			
BMI (kg/m^2)	*0.56***	1			*0.64***	1			*0.43***	1		
WHR	*0.29***	0.07	1		0.17	0.16	1		*0.37***	0.07	1	
Total Body Fat (%)	*0.43***	*0.56***	−0.02	1	*0.31**	*0.28**	0.10	1	*0.23***	*0.19**	−0.13	1
Android Body Fat (%)	*0.37***	*0.58***	−0.03	*0.77***	0.33	0.28	−0.04	*0.66***	0.22	*0.40***	0.01	*0.69***
Gynoid Body Fat (%)	0.13	*0.41***	*−0.23**	*0.54***	−0.06	−0.06	−0.25	0.16	0.09	*0.41***	*−0.25**	*0.75***
Systolic BP (mm Hg)	*0.34***	*0.29***	*0.23***	0.08	*0.33**	0.19	*0.36**	−0.10	*0.32***	*0.33***	0.18	0.08
Diastolic BP (mm Hg)	*0.38***	*0.26***	0.09	0.08	*0.29**	*0.43***	0.13	0.08	*0.41***	*0.32***	0.06	0.08
Glucose (mmol/l)	*0.31***	−0.02	*0.20**	*−0.19**	*0.27**	0.14	0.13	*−0.37**	*0.40***	0.02	*0.24**	−0.08
TG (mmol/l)	*0.32***	0.07	*0.35***	−0.04	*0.38***	*0.34**	*0.36**	−0.17	*0.28***	0.01	*0.33***	−0.03
HDL-C (mmol/l)	−0.15	−0.03	−0.15	0.02	−0.16	−0.10	−0.15	0.11	−0.10	0.10	−0.13	0.11
25(OH)D (nmol/l)	*−0.17**	−0.12	−0.09	−0.03	−0.23	*−0.31**	−0.10	−0.10	−0.10	−0.05	−0.10	0.11
Rankl (pg/ml)	−0.01	−0.02	*0.19**	−0.12	−0.01	−0.15	0.22	0.01	−0.01	0.01	0.17	−0.14
SOST (pg/ml)	−0.01	−0.12	0.21	−0.13	−0.10	0.04	−0.04	−0.07	−0.02	−0.15	0.25	−0.15
CTX-I (pg/ml)	−0.13	−0.02	0.14	0.13	0.17	0.23	0.18	0.20	−0.28	−0.05	0.19	0.16
PTH (pg/ml)	*−0.22**	−0.10	0.05	−0.05	0.03	0.28	*−0.50**	0.31	*−0.37***	−0.03	0.16	−0.05
Dkk1 (pg/ml)	−0.05	*−0.22**	*0.32***	−0.17	0.01	−0.33	0.19	−0.40	−0.07	−0.18	*0.30**	−0.05
IL1β (pg/ml)	0.05	0.10	*−0.25**	−0.03	0.04	0.10	−0.14	0.14	0.10	0.13	−0.26	−0.06
OPG (ng/ml)	*0.20**	−0.10	0.12	0.10	0.05	−0.27	0.31	0.06	0.19	*−0.29**	−0.04	−0.05
OPN (ng/ml)	0.01	−0.07	0.05	0.12	0.02	0.18	0.16	*0.45**	−0.10	−0.23	−0.02	0.01
OC (ng/ml)	−0.02	−0.04	−0.06	0.05	−0.15	−0.10	−0.12	0.10	0.04	−0.12	−0.03	−0.04
PINP (ng/ml)	−0.06	−0.05	0.19	−0.04	0.01	0.04	0.16	0.07	−0.06	0.01	0.19	−0.03

Data presented as coefficient (R); significant associations are in italics; *denotes significance at 0.05 level; **denotes significance at 0.01 level. Coefficients were adjusted for age and menopausal status; the italics are only to emphasize that the entries were significant (< 0.05)

Table 3 Clinical characteristics of participants according to menopausal status

Parameters	Pre-menopausal	Post-menopausal	*p* value	Adjusted for Age
N	151	114		
Age (years)	48.2 ± 6.9	55.4 ± 6.8	*< 0.001*	
BMI (kg/m^2)	33.1 ± 5.7	32.5 ± 5.7	0.42	0.92
NC (cm)	36.7 ± 2.6	35.9 ± 2.2	*0.01*	*0.003*
WHR	0.90 ± 0.10	0.93 ± 0.10	0.07	0.77
Total body fat (%)	47.1 ± 4.8	46.1 ± 4.7	0.13	0.19
Body fat (%), android	49.9 ± 5.8	48.8 ± 5.9	0.34	0.41
Body fat (%), gynoid	48.2 ± 4.0	47.7 ± 6.4	0.60	0.91
Systolic blood pressure (mmHg)	123.3 ± 19.1	125.5 ± 15.9	0.31	0.71
Diastolic blood pressure (mmHg)	74.5 ± 11.0	74.3 ± 10.9	0.84	0.58
Glucose (mmol/l)#	7.3 ± 3.1	7.1 ± 3.1	0.51	0.47
Total cholesterol (mmol/l)	5.11 ± 1.0	5.10 ± 0.8	0.84	0.79
HDL-cholesterol (mmol/l)	1.23 ± 0.3	1.28 ± 0.3	0.39	0.26
LDL-cholesterol (mmol/l)	3.1 ± 1.0	3.1 ± 0.9	0.93	0.44
Triglycerides (mmol/l)#	1.5 (1.2–2.1)	1.5 (1.2–2.0)	0.73	0.49
25(OH)D (nmol/l)#	69.7 (39.5–99.5)	82.5 (60.2–106.1)	*0.005*	0.08
Rankl (pg/ml)#	32.6 (20.9–64.4)	33.9 (23.1–51.9)	0.96	0.56
SOST (ng/ml)#	2.1 (1.3–3.1)	2.3 (1.7–3.1)	0.42	0.74
CTX-I (pg/ml)#	20.0 (10.0–70.0)	40.0 (10.0–70.0)	0.43	0.55
PTH (pg/ml)#	16.7 (11.2–22.1)	17.5 (11.4–28.3)	0.66	0.69
Dkk1 (μg/ml)	2.8 ± 1.2	3.3 ± 1.2	*0.05*	0.25
IL1β (pg/ml)#	1.6 (0.3–2.6)	0.3 (0.2–1.5)	*0.02*	*0.04*
OPG (ng/ml)	0.63 ± 0.24	0.72 ± 0.26	0.48	0.83
OPN (ng/ml)#	2.9 (1.7–4.9)	4.5 (1.6–6.8)	0.26	0.45
OC (ng/ml)	8.7 ± 6.11	8.4 ± 5.7	0.79	0.39
PINP (ng/ml)#	16.4 (7.0–32.2)	18.5 (5.6–26.7)	0.98	0.85

The number sign denotes non-normal variable and is presented as median; data presented as mean ± SD for normal variables while median (quartile 1–quartile 3) for non-normal variables; *p* values < 0.05 considered significant; the italics are only to emphasize that the entries were significant (< 0.05)

Table 4 shows the bivariate associations of NC with all variables based on menopausal status. In the pre-menopausal group, NC was inversely associated with PTH ($R = -0.35$; $p < 0.05$) and positively associated with OPG ($R = 0.33$; $p < 0.05$). NC was not associated with any bone biomarkers in the post-menopausal group.

Table 5 shows the regression analysis using CTX-I as dependent variable and the major anthropometric indices [NC, BMI, WHR, and total body fat (%)] as independent markers. While the entire model explained 31.7% of the variance perceived, only NC explained this variance in CTX-I ($p = 0.049$). No significance was found using other bone markers as dependent variables. Furthermore, using android fat percentage as independent variable instead of NC showed no significance and explained only 20.5% of the variance perceived in CTX-I levels (not shown in table).

Lastly, Fig. 1 shows the significant inverse association of CTX-I and NC only in the obese group ($R = -0.28$; $p = 0.016$). This inverse association remained significant after adjustment for age ($R = -0.24$; $p = 0.028$), but lost significance after adjusting for both age and menopausal status ($R = -0.21$; $p = 0.18$) (Table 2).

Discussion

The present cross-sectional study is, to the best of our knowledge, the first observational study to ascertain whether NC is associated with BTMs and whether such adiposity index is superior to other conventional measures of obesity with respect to altering bone-regulating hormones. NC, a marker for upper body fat distribution that can be further explored as a measure of obesity, has never been tested as a parameter potentially influencing or reflecting bone turnover, given that body fat distribution and obesity as a whole decreases bone resorption [11] and that body fat sequesters or entraps circulating vitamin D [12]. Highlights of the study include significant associations between NC with PTH and OPG in all participants, CTX-I in obese participants, as well as the lack of

Table 4 Associations of NC with other parameters according to menopausal status

Parameters	Pre-menopausal ($N = 151$)				Post-menopausal ($N = 114$)			
	NC	BMI	WHR	BF	NC	BMI	WHR	BF
NC (cm)	1				1			
BMI (kg/m^2)	*0.53***	1			*0.50***	1		
WHR	*0.23***	0.01	1		*0.20**	− 0.08	1	
Total body fat (%)	*0.32***	*0.56***	0.04	1	*0.45***	*0.56***	− 0.16	1
Android body fat (%)	*0.33**	*0.66***	− 0.27	*0.85***	*0.47***	*0.56***	0.10	*0.72***
Gynoid body fat (%)	*0.32**	*0.64***	*− 0.37***	*0.88***	0.09	*0.37***	*− 0.22*	*0.44***
Systolic BP (mm Hg)	*0.38***	*0.35***	0.07	*0.23***	*0.37***	*0.22**	*0.23**	0.03
Diastolic BP (mm Hg)	*0.37***	*0.27***	− 0.06	0.17	*0.32***	*0.21**	− 0.10	0.10
Glucose (mmol/l)	*0.37***	0.02	0.14	− 0.18	*0.31***	0.05	*0.19**	− 0.06
TG (mmol/l)	*− 0.17**	− 0.10	− 0.10	0.02	− 0.17	− 0.09	*− 0.32***	− 0.02
HDL-C (mmol/l)	*0.30***	0.13	0.16	0.17	*0.24**	0.01	*0.42***	− 0.14
25(OH)D (nmol/l)	*− 0.21***	− 0.14	− 0.01	0.07	− 0.14	− 0.08	− 0.13	− 0.03
Rankl (pg/ml)	− 0.01	− 0.02	0.03	0.01	− 0.02	− 0.13	*0.27***	− 0.21
SOST (pg/ml)	0.03	0.05	*0.32**	− 0.03	− 0.01	− 0.29	0.11	− 0.25
CTX-I (pg/ml)	− 0.22	− 0.04	0.03	0.06	− 0.03	− 0.08	0.17	0.20
PTH (pg/ml)	*− 0.35**	0.17	− 0.12	0.16	− 0.10	*− 0.37**	0.10	− 0.31
Dkk1 (pg/ml)	0.02	0.01	*0.38***	− 0.08	0.01	*− 0.46***	0.14	− 0.31
IL1β (pg/ml)	0.07	− 0.15	− 0.21	− 0.03	0.03	*0.33**	− 0.20	− 0.02
OPG (ng/ml)	*0.33**	0.01	0.17	0.02	0.18	− 0.10	0.10	0.12
OPN (ng/ml)	0.04	*0.32**	0.15	0.26	− 0.12	*− 0.48***	0.01	− 0.07
OC (ng/ml)	− 0.07	0.10	− 0.13	0.10	− 0.01	− 0.17	0.06	− 0.04
PINP (ng/ml)	− 0.10	− 0.01	0.22	− 0.03	− 0.21	− 0.25	0.11	− 0.07

Data presented as coefficient (R); *denotes significance at 0.05 level; **denotes significance at 0.01 level. Coefficients were adjusted for age; the italics are only to emphasize that the entries were significant (< 0.05)

any significant association between BMI, WHR, and body fat to all BTMs measured in the obese participants.

With regard to the modest but significant associations of select BTMs, circulating CTX-I levels and OPG were found to be inversely and positively associated with NC, respectively. CTX-I is one of the degradation products of type 1 collagen and OPG (together with Dkk1, RANKL, and SOST) is considered an osteocyte activity marker [13]. Serum CTX-I is of particular interest because similar to obesity, CTX-I is highly influenced by circadian rhythm and food intake, both of which if disrupted alters over-all human glucose, lipid and energy metabolism [14, 15]. A possible mechanism of the lower CTX-I level in women with higher NC is the higher peripheral synthesis of estrogens which decrease bone resorption [16]. Circulating levels of OPG was also significantly associated with NC. OPG belongs to the tumor necrosis-factor family and classified as an anti-resorptive hormone that binds to RANKl [17]. OPG has been observed to be an active cytokine with multiple functions independent of its role in skeletal health, including increased expression in known chronic non-communicable diseases such as diabetes, hypertension, atherosclerosis, metabolic syndrome, and obesity [18, 19]. It makes sense therefore since NC, being associated with decreased bone turnover, is inversely associated with CTX-I and positively associated OPG which, in turn, induces apoptosis in the osteoclasts.

Table 5 Multiple regression analysis using CTX-I as dependent variable

Model	β	95% confidence interval (CI)		p value
		Lower bound	Upper bound	
(Constant)	0.02	− 0.045	0.080	0.58
NC (cm)	− 0.002	− 0.003	0.001	*0.049*
BMI (kg/m^2)	0.00	− 0.001	0.001	0.65
WHR	0.03	− 0.012	0.071	0.16
Body fat (%)	0.001	0.000	0.002	0.10

Independent variables included NC, BMI, WHR, and total body fat (%); the italics are only to emphasize that the entries were significant (< 0.05)

As for other significant associations with adiposity indices in the study, OPN, a multi-functional non-collagenous protein involved in matrix remodeling and bone calcification [20], was found to be significantly associated with body fat (%) among non-obese individuals. SOST and Dkk1, both of which

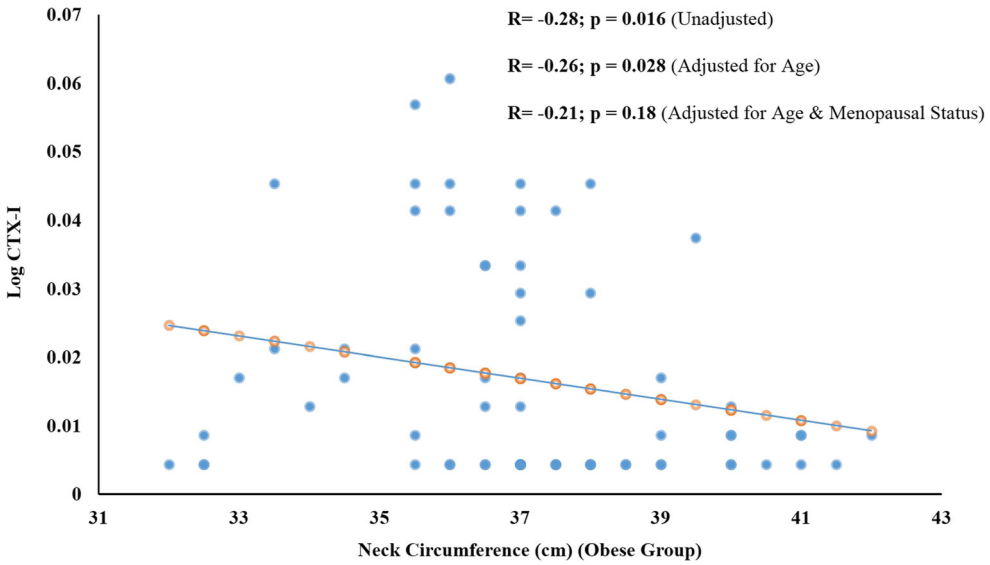

Fig. 1 Inverse association between NC and CTX-I among obese participants

are bone resorption markers intricately involved in the Wnt signaling transduction pathways known to promote adiposity-induced inflammation independent of increasing fat mass [21–23], were found to be positively associated with WHR in all participants. These significant but modest associations in the present study, although in select fat depots, nevertheless suggest cross-talk dynamics between bone and fat metabolism. Other significant associations of NC to cardiometabolic parameters and adiposity indices elicited in the present study will not be discussed as majority, if not all of them, have been established previously. Evidence on the clinical use of NC so far has been limited as a surrogate measure of obesity and several cardiovascular risk factors, including metabolic syndrome, in several populations and ethnic groups [24–27]. NC as a depot for upper body subcutaneous fat is also highly correlated with visceral (central) adiposity and arterial stiffness among obese individuals [28], both of which (central adiposity and arterial stiffness) are inversely associated with BMD of the femur, an indicator of hip fracture risk [29, 30].

The authors acknowledge several limitations. The small sample size may have affected the results and adjusted correlations in particular. Further studies on other adult populations including men should be investigated. Also, as the over-all metabolic profile of the cohort were unaccounted for, confounding variables such as medical history and medicine use which can potentially affect circulating BTMs, including lifestyle factors (e.g., nutritional habits, housework-related physical activity) should have been included. Lastly, although the prevalence of menopausal participants were equally distributed in both groups, the effects of menopause in the present results remain unclear as it has been documented in several studies that estrogen status would be expected to mask any smaller effect of obesity on BTMs [31–33].

Despite several limitations, this is the first study to determine associations between NC and markers of bone metabolism and findings were discussed in light of other evidence with respect to obesity and regional distribution of adiposity as measured by other conventional indices. The present study confirms that abnormal distribution of fat influences expression of BTMs and NC, being an adiposity index for upper subcutaneous fat, modestly influences expression of these BTMs.

In conclusion, NC is significantly associated with several markers of bone metabolism, particularly OPG and CTX-I among adult Saudi women. Further studies using a larger population should be done to confirm present cross-sectional findings.

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Compliance with ethical standards

Written informed consent was obtained from each participant prior to inclusion. Ethical approval was obtained from the Ethics Committee of the College of Science in KSU, Riyadh, KSA.

Conflicts of interest None.

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