Oxidative damage and associated inflammatory risk factors in obese Emirati women

Body mass index versus waist circumference

Salah Gariballa, *MD, FRCP,* ***Juma Alkaabi,*** *MD, FRCP,* ***Javed Yasin,*** *BSc,* ***Awad Al Essa,*** *BSc,*

ABSTRACT

الأهداف: تحديد ما إذا كان مؤشر كتلة الجسم أو محيط الخصر هو أفضل مؤشر لعوامل الخطر الأيضية المرتبطة بزيادة الدهون المتواجدة في الكرش بين النساء البدينات في دولة الإمارات العربية المتحدة.

الطريقة: توجد 333 حالة من الذين يعانون من السمنة المفرطة وقد كانت هذه الحالات جزءا من دراسة التدخل الغذائية تم فيها وضع المعيار الأساسي وفقاً لتقييم بيانات القياسات البشرية والسريرية والكيميائية الحيوية، وذلك بعد الحصول على الموافقة الخطية. تم جمع عينات من الدم أثناء الصيام لقياس أي مؤشرات لوجود اللالتهاب، اختلال الأغشية الوظيفي، ومضادات الأكسدة وأضرار الأكسدة. وتمت مقارنة قياسات النتائج بين 4 من الحالات التي تساوى فيها مؤشر كتلة الجسم ومحيط الخصر الرباعي.

النتائج: لاحظنا إرتفاع ضغط الدم بشكل ملحوظ، وإرتفاع نسبة البروتين في الدم، وإرتفاع كربونيلات البروتين وانخفاض مستويات الكاروتين مع زيادة مؤشر كتلة الجسم ومحيط الخصر. وقد كانت نسبة كل من الجلوتاثيون بيروكسيديز (تتمثل وظيفته في الحماية من الضرر التأكسدي) واديبونيكتين (سيتوكين دهني) منخفضة، مع إرتفاع عامل نخر الورم ألفا (بروتين يشارك في عملية الالتهاب في جسم الإنسان) مع زيادة محيط الخصر مقارنة مع زيادة مؤشر كتلة الجسم الربعية، ولكن النتائج كانت فقط ذات دلالة إحصائية لعامل نخر الورم ألفا.

الخاتمة: يرتبط كلاً من ارتفاع مؤشر كتلة الجسم ومحيط الخصر مع زيادة عوامل الخطر الأيضية في المرأة الإماراتية التي تعاني من السمنة المفرطة، ولكن محيط الخصر يشكل مؤشرا أقوى بالمقارنة مع مؤشر كتلة الجسم.

Objectives: To establish whether body mass index (BMI) or waist circumference (WC) is a better predictor of cardio metabolic risk factors that are associated with increased visceral fat among obese women from the United Arab Emirates (UAE).

Methods: In this Cross-sectional study, 333 obese subjects visiting community health centers in Al Ain city, UAE, were recruited between 2012 and 2015. After a written consent subjects had anthropometric, clinical and biochemical measurements. Fasting serum and plasma samples were collected for the measurement of markers of oxidative damage, antioxidants and inflammation. Outcome measures were compared between 4 equal BMI and WC quartiles.

Results: We observed significantly higher blood pressure, c-reactive protein levels, IL6 levels, and protein carbonyls contents and lower β-carotene levels in the fourth quartile than in the first quartile for both BMI and WC (p<0.01). Glutathione peroxidase and adiponectin both decreased and TNF-α increased with increasing WC quartiles but not BMI quartiles; however, the results were statistically significant only for TNF-α (p=0.032).

Conclusion: Both elevated BMI and elevated WC are associated with increased cardio metabolic risk factors in obese Emirati women; however, WC is a stronger predictor than is BMI.

Saudi Med J 2017; Vol. 38 (9): 960-964
doi:10.15537/smj.2017.9.19629

From the Department of Internal Medicine, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates.

Received 22nd February 2017. Accepted 26th June 2017.

Address correspondence and reprint request to: Dr. Salah Gariballa, Department of Internal Medicine, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates. E-mail:s.gariballa@uaeu.ac.ae ORCID:orcid.org/0000-0002-0069-6322

Disclosure. Authors have no conflict of interest, and the work was not supported or funded by any drug company. This study was funded by the Emirates Foundation and a project grant from the National Research Foundation/ United Arab Emirates University, Al Ain, United Arab Emirates. (Grant No. 10/049)

Obesity is a known risk factor for chronic diseases including type 2 diabetes, hypertension and cardiovascular disease (CVD).[1-3] In the Gulf region, the prevalence of obesity is increasing, and in some countries such as the United Arab Emirates (UAE), obesity is a major public health problem.[1-4] Recent studies suggest that abdominal/visceral obesity as determined by waist circumference (WC) is closely related to chronic diseases associated with obesity, especially in the Middle East.[5-9] An International study that included subjects from the Middle East assessed the relationships of BMI and WC to CVD reported that globally, the waist-to-hip is strongly related to the risk of myocardial infarction.[8,9] If increased WC was used to assess the risk of CVD in the Middle East, the number of people classified as obese would increase significantly.[8] Furthermore, the results suggested that BMI was uninformative for assessing CVD risk in the Arabs, highlighting the need for the present study.[8,9] A number of inflammatory cytokines secreted by visceral fat have been implicated in obesity-related complications.[3,10] Oxidative damage and inflammation are possible mechanisms linking obesity to diabetes and CVD risk. For example, oxidative stress has been found to correlate with increased inflammation in obese patients, and this may be the mechanism underlying obesity-related insulin resistance. Although the UAE has one of the highest rates of obesity and related diabetes mellitus in the world, the factors that affect obesity and associated diseases in this region, remain unclear. In this cross-sectional study, we examined whether BMI or WC is a better predictor of metabolic risk factors including oxidative damage, endothelial dysfunction, and inflammatory markers among obese women from the UAE.

Methods.

Overweight and obese female subjects (BMI >25) visiting community health centers in the city of Al Ain, UAE, between 2012 and 2015 were invited to take part in the study. After informed written consent was obtained from the eligible subjects, the subjects underwent baseline assessment, which included anthropometric measurements and 10-ml fasting blood samples collected to measure markers of antioxidants, oxidative damage and inflammation. Other related biochemical variables, including endothelial dysfunction, were also measured. The exclusion criteria were severe chronic disease and use of anti-obesity medications. Al Ain Medical District Human Research Ethics Committee approved the study (protocol number 09/70), and written consent was obtained from each subject recruited to the study.

Measurements. All participants underwent baseline clinical assessment to record medical and clinical data, including history of chronic disease, medications and smoking history. The Tanita body composition analyzer was used to assess height, body weight, and fat mass. Waist circumference was measured using a flexible plastic tape to the nearest 0.1 cm.

Blood samples. Blood samples were taken in tubes containing potassium EDTA and anticoagulant, thoroughly mixed at room temperature and immediately transferred to the laboratory. Following centrifugation for 10 min at 4000 rotations/minutes, both plasma and serum tubes were stored at -80°C.

Antioxidants. Vitamin E and beta-carotene analyses were carried using HPLC [Waters (Milford, MA) system gradient liquid chromatography pump (model 515)]. Commercially available Cayman's colorimetric assay kits from USA-Kit numbers 706002, 707002, and 703102 were used to measure antioxidant enzymes, including glutathione (GSH), superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase. Inflammatory markers (TNF, IL6 and adiponectin) and markers of endothelial dysfunction vascular cell adhesion molecule-1 (v-CAM) and intracellular adhesion molecule (i-CAM) were measured using enzyme-linked immunosorbent assay (ELISA) kits.

Lipid peroxidation. The lipid peroxidation product thiobarbituric acid-reactive substances (TBARS) was measured using an assay kit "no. 10009055" (Cayman, 1180 E. Ellsworth Rd., Ann Arbor, MI 48108.

Protein oxidation. Protein oxidation was assessed measuring protein-bound carbonyls calorimetrically using a reagent kit (no. 10005020) from Cayman Chemical. Circulating levels of renal and liver functions, lipids, high sensitivity C-reactive protein (hsCRP), vitamin B12 and serum folate were measured using an Integra 400 Plus automated analyzer (Roche Diagnostics, Mannheim, Germany).

The Statistical Package for the Social Sciences (IBM Corp., Armonk, NY) version 19 was used for statistical analyses. BMI and WC were divided into 4 equal quartiles. For within and among-group differences we used One-way ANOVA or Kruskal-Wallis H depending on data distribution, and a p value < 0.05 was considered significant.

Results.

A total of 333 overweight or obese female subjects were recruited and included in this analysis. Their mean ±SD age was 36±11 years. Based on the WHO non-Asian population sex-adjusted cut-off points for BMI, 76 (23%) of the 333 female subjects were at high health risk [BMI 25.1-29.9], and 257 (77%) were at increased health risk [BMI ≥30]. Based on the corresponding waist circumference cut-off points, 43 (13%) subjects

were at high risk [WC=81-88 cm], 257 (77%) [WC >88 cm] were at increased health risk, and 20 (6%) subjects had satisfactory WC [≤80 cm].

Table 1 shows the baseline demographic and clinical characteristics of obese female subjects according to BMI and WC divided into 4 quartiles. The number of subjects who have had more education and the number in employment were significantly higher in the first quartile than in the fourth quartile of the distribution for both BMI and WC (p<0.05). Systolic and diastolic blood pressure were both significantly lower in the first quartile than in the fourth quartile of the distribution for both BMI and WC (p< 0.05).

Levels of inflammatory, endothelial dysfunction, antioxidant and oxidative damage markers according to BMI and WC quartiles are shown in (**Tables 2** & **3**). The levels of hs-CRP, IL6, and protein carbonyl were clearly and significantly increased and that of β-carotene was decreased at the fourth quartile relative to the first quartile of the distribution for both BMI (**Table 2**) and WC (**Table 3**) (p<0.01). The TNF and glutathione levels were higher and adiponectin and glutathione peroxidase levels were lower in the fourth quartile than in the first quartile of the distribution for WC (**Table 3**), but not BMI quartiles (**Table 2**); however, a significant difference was only observed for TNFα. No significant difference in endothelial dysfunction marker levels, vitamin B12 or folate was observed between the first and fourth quartiles for either WC or BMI.

Discussion. We observed increased levels of inflammation and oxidative damage markers and decreased levels of antioxidant markers with increasing BMI and WC quartile number; however, the levels of some metabolic risk markers were significantly higher at higher WC quartiles but not at higher BMI quartiles. Increased BMI is used to measure obesity; however, recent work suggests that abdominal obesity, which is more prevalent in the UAE region, is more closely associated with chronic disease.[5-7] as BMI does not account for factors such as body size and body fat distribution. It is believed that a high WC, which reflects abdominal/visceral obesity, is more closely related to morbidity because visceral fat secretes several metabolically active that are involved in the diseases related to obesity.[3,10,11] In a small, recent study, we observed trends of increasing inflammatory marker levels and decreasing antioxidant levels with increasing WC; however, these trends were significant in women only.[12] Oxidative damage and inflammation are potential mechanisms that link obesity to increased risk of related chronic diseases. For example, markers of oxidative stress have been found to correlate with inflammatory markers in adipose tissue of obese patients; this might be the mechanism for obesity-related complications.[13,14] Oxidative stress is defined as the imbalance between the generation of free oxygen radicals and the antioxidant defense system and is known to generate reactions that damage membrane

Table 1 - Baseline demographic and clinical characteristics of obese female subjects according to quartiles of body mass index (BMI) and waist circumference (WC), mean (SD).

Variables	1st quartile		2nd quartile		3rd quartile		4th quartile	
	BMI n=118	WC n=90	BMI n=51	WC n=51	BMI n=92	WC n92	BMI n=72	WC n=82
Age (years) (mean±SD)	35±10	34±10	37±10	34±10	36±11	39±11	38±12	39±12
Marital status								
Single	29	27	9	19	22	14	20	20
Married	74	52	38	52	59	58	36	45
*Education (n)**								
illiterate	10	5	6	6	7	9	12	15
Primary	10	9	10	12	8	15	11	13
Secondary	36	29	16	20	25	26	29	32
University	50	35	5	31	36	31	18	21
Post Graduate	3	3	0	4	3	3	2	1
*Employment (n) **								
Employed	31	24	6	14	18	17	16	16
Previous diabetes (n)	11	8	4	3	6	8	10	12
Previous hypertension (n)	9	8	6	7	16	13	15	18
Cholesterol-lowering medications (n)	3	2	3	1	5	6	2	4
Other medications (n) (mean±SD)	3	3	3	2	3	1	4	2
Systolic BP (mmHg)* (mean±SD)	117±13	116 (12)	119±13	119±13	120±13	122±13	123±18	122±13
Diastolic BP (mmHg)* (mean±SD)	71±8	71 (8)	72±8	72±8	75±10	74±9	73±9	74±10
Fasting blood glucose (mean±SD)	5.5±1.4	5.4 (0.7)	5.4±0.7	5.5±1.6	5.4±0.9	5.4±0.8	6.3±1.9	6.1±1.9

Eighteen subjects with missing WC were excluded from analysis. * p-value ≤0.05 for the difference within or among BMI or WC quartiles

proteins and lipids. Several recent studies have suggested close associations between oxidative stress and complications of diabetes, signifying an important role of oxidative stress in the pathology and progression of the disease.[13] Furthermore, a relationship between oxidative stress and insulin resistance has been reported, suggesting that antioxidants may reduce insulin resistance.[14] Dietary antioxidants may also be predictors of some risk factors in healthy subjects as evaluated by inflammatory biomarkers, blood pressure and plasma glucose.[15] For example, a meta-analysis concluded that increasing dietary intake of vegetables could reduce the risk of type 2 diabetes.[16] Taken together, these results suggest that increased fruit and vegetable intake may

Table 2 - Markers of inflammation, endothelial dysfunction, oxidative damage and antioxidants according to body mass index (BMI) divided into 4 equal quartiles.

Biochemical Measurements	BMI				
	1st quartile BMI 25-30 (n=118)	2nd quartileBMI 30.1-32 (n=51)	3rd quartileBMI 32.1-37(n=92)	4 quartileBMI ≥ 37.1(n=72)	*P*-value
CRP (mg/l)	4.9±4.8	6.2±5.6	6.8±5.8	12.2±10.2	0.000*
IL6 (pg/ml)	2.3±2	2.6±1.9	2.5±1.4	3.6±2.5	0.011*
TNFα (pg/ml)	1.37±0.4	1.28±0.5	1.42±0.4	1.50±0.9	0.096
Adiponectin (µg/ml)	6.2±3	5.7±3.3	6.3±3.4	6.5±3.8	0.768
i-CAM (ng/ml)	210±(40	221±48	213±49	219±52	0.594
v-CAM (ng/ml)	570±145	592±137	562±151	592±149	0.689
Vitamin B12 (pmol/l)	486±279	405±164	424±185	413±175	0.197
Folate (nmol/l)	10.9±5	10.9±4.3	10.3±3.6	9.3±3.5	0.286
Vitamin E (mg/l)	6.2±3.2	6.9±4	6.8±4.8	5.9±3.8	0.742
β-carotene (µg /ml)	0.299±0.24	0.195±0.19	0.151±0.08	0.142±0.11	0.009*
Superoxide dismutase (U/ml)	4.3±2.8	3.5±1.9	3.8v1.9	3.7±1.6	0.342
Catalase (nmol/min/ml)	27±15	23±10	27±13	29±17	0.257
Glutathione peroxidase (ng/ml)	67±110	46±14	50±22	43±14	0.248
Glutathione (nM/ml)	6.32±4.6	6.34±3.3	6.88±4.5	5.60±2.9	0.538
Antioxidant capacity (mM)	5.62±2.3	5.52±2.2	5.58±1.7	5.6±1.9	0.997
Protein carbonyl (nmol/mg)	0.06±0.05	0.07±0.05	0.08±0.08	0.10±0.07	0.001*
TBARS (nmol/ml)	2.93±1.7	3.16±1.2	3.30±1.4	3.26±1.5	0.434

CRP - +C-reactive proteins, i-CAM - intracellular adhesion molecule , v-CAM - vascular cell adhesion molecule-1 , TBARS - thiobarbituric acid-reactive substances , * *p*-value ≤0.05 for the difference among BMI quartiles determined using ANOVA, values are Mean±SD

Table 3 - Markers of inflammation, endothelial dysfunction, oxidative damage, and antioxidants according to waist circumference (WC) divided into 4 equal quartiles.

Biochemical Measurements	WC				
	1st quartile WC ≤ 90 cm (n=90)	2nd quartile WC 91-97 cm (n=51)	3rd quartile WC 98-107 cm (n=92)	4 quartile WC ≥108 cm (n=82)	*P*-value
CRP (mg/l)	4.9±4.7	5.3±5.5	7.3±6.2	11.1±9.7	0.000*
IL6 (pg/ml)	2.2±1.6	2.2±1.4	2.7±2.2	3.5±2.3	0.003*
TNFα (pg/ml)	1.33±0.5	1.34±0.8	1.37±0.5	1.54±0.7	0.032*
Adiponectin (µg/ml)	6.85±3.7	6.55±3.2	5.85±3.3	5.51±2.8	0.173
i-CAM (ng/ml)	214±42	216±41	215±56	214±47	0.997
v-CAM (ng/ml)	604±159	589±138	557±129	554±152	0.246
Vitamin B12 (pmol/l)	427±254	428±150	476±256	426±188	0.582
Folate (nmol/l)	11.4±5	10.3±3.9	10.2±4.1	9.6±3.7	0.208
Vitamin E (mg/l)	5.8±2.7	6.7±4.3	7.6±4.8	5.4±2.9	0.088
β-carotene (µg /ml)	0.351±0.3	0.188±0.10	0.170±0.11	0.132±0.9	0.000*
Superoxide dismutase (U/ml)	3.6±1.9	4.3±2.3	4.2±2.6	3.5±1.8	0.178
Catalase (nmol/min/ml)	25.0±16.5	26.6±11.6	26.8±14	28.3±14	0.734
Glutathione peroxidase (ng/ml)	60±96	52±43	58±78	45±14	0.697
Glutathione (GSH) (nM/ml)	5.57±3.4	7.54±4.7	6.08±4.3	6.25±3.7	0.119
Antioxidant capacity (mM)	5.28±2.1	5.54±2.4	5.90±1.9	5.60±2.1	0.498
Protein carbonyl (nmol/mg)	0.06±0.05	0.07±0.05	0.07±0.06	0.10±0.06	0.000*
TBARS (nmol/ml)	3.01±1.4	3.33±1.3	2.90±1.3	3.37±1.3	0.213

* *P*-value ≤0.05 for the difference among WC quartiles determined using ANOVA, values are Mean±SD

be important for mitigating the deleterious effects associated with visceral obesity.

A recent study revealed that higher consumption of red/purple fruit and vegetables, such as berries, strawberry, and red plum was associated with lower abdominal fat gain.[17] Another study reported a beneficial effect of higher intake of fruits, vegetables and cereal fiber on abdominal obesity prevention.[18] The effects of fruits and vegetables on visceral obesity might be mediated by a decreased inflammatory response, the mitigation of oxidative damage associated with inflammatory cytokines that favor lipolysis and lipid oxidation instead of fat storage.[19,20] This is clearly an area for further research.

Although the roles of both oxidative damage and related inflammation in the development of chronic complications in obese patients are well accepted, the benefits of increased fruit and vegetable consumption in the treatment of visceral obesity and related complications, including type 2 diabetes mellitus, have not been sufficiently studied.[21]

In conclusion, the above results suggest that the levels of oxidative stress and inflammatory markers are higher in obese women than non-obese women and increase with increasing WC. We are not aware of any previous studies that have attempted to measure the prevalence of cardio-metabolic risk factors, for example, by measuring antioxidant enzymes and oxidative markers, in relation to BMI and WC in obese women from the Middle East. Interventions that mitigate oxidative damage and/or reduce inflammation could be essential for reducing or preventing obesity and related chronic disease. Increased intake of dietary supplements notable fruits and vegetables may be an innovative strategy for controlling and reducing the obesity epidemic. Studies on dietary factors that are known to mitigate oxidative stress and inflammation and also promote health are urgently needed in this population.

References

1. World Health Organisation, Obesity: Obesity: preventing and managing the global epidemic Report of a WHO Consultation (WHO Technical Report Series 894). Geneva (SW): WHO: (2000).
2. McLellan, Obesity rising to alarming levels around the world. ***Lancet*** 2002; 359: 1412.
3. Stanner S. Cardiovascular Disease: Diet, Nutrition and Emerging Risk Factors (The Report of the British Nutrition Foundation Task Force). Oxford: Balckwell Publishing Ltd; 2005.
4. Malik A, Babir A, Abi Saab B, Roglic G, King H. Glucose intolerance and associated factors in the UAE. ***Diabetes Research & Clinical Practice*** 2005; 69: 188-195.
5. Baik I, Ascherio A, Rimm EB, Giovannucci E, Spiegelman D, Stampfer MJ, et al. Adiposity and mortality in men. ***Am J Epidemiol*** 2000 1;152: 264-271.
6. Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, Stampfer MJ. Abdominal adiposity and coronary heart disease in women, ***JAMA*** 1998; 280: 1843-1848.
7. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies, ***Lancet*** 2004; 363: 157-163.
8. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, et al. Obesity and risk of myocardial infarction in 27 000 participants from 52 countrries: A case-control study. ***Lancet*** 2006; 366: 1640-1649.
9. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. ***Lancet*** 2004; 364: 937-952.
10. Trayhurn P. Bology of obesity. ***Proceedings of the Nutrition Society*** 2005; 64: 31-38.
11. Gariballa S, Afandi B, Abuhaltem M, Yassin J, Habib H, Ibrahim W. Oxidative damage and inflammation in obese diabetic Emirati subjects supplemented with antioxidants and B-vitamins. ***Nutr Metab (Lond)*** 2013 4; 10: 21.
12. Gariballa S, Kosanovic M, Yasin J, Essa AE, Oxidative damage and inflammation in obese diabetic emirati subjects. ***Nutrients*** 2014; 6: 4872-4880.
13. Hill MF. Emerging role for antioxidant therapy in protection against diabetic cardiac complications: Experimental and clinical evidence for utilization of classic and new antioxidants. ***Curr Cardiol Rev*** 2008; 4: 259-268.
14. Evans JL. Antioxidants: do they have a role in the treatment of insulin resistance? ***Indian J Med Res*** 2007; 125: 355-372.
15. Puchau B, Zulet A, Gonzalez A, Hermsdorff H, Martinez J. Dietary total antioxidant capacity is negatively associated with some metabolic syndrome features in healthy young men. ***Nutrition*** 2010; 26: 534-541.
16. Carter P, Gray LJ, Troughton J, Khunti K, Davies MJ. Fruit and vegetable intake and incidence of type 2 diabetes mellitus: systematic review and meta-analysis. ***BMJ*** 2010; 341: c4229.
17. Mirmiran P, Bahadoran Z, Moslehi N, Bastan S, Azizi F. Colors of fruits and vegetables and 3-year changes of cardiometabolic risk factors in adults: Tehran lipid and glucose study. ***Eur J Clin Nutr*** 2015; 69: 1215-1219
18. Du H, van der A DL, Boshuizen HC, Forouhi NG, Wareham NJ, Halkjaer J, et al. Dietary fiber and subsequent changes in body weight and waist circumference in European men and women. ***Am J Clin Nutr*** 2010; 91: 329-36.
19. Katcher HI, Legro RS, Kunselman AR, Gillies PJ, Demers LM, Bagshaw DM, et al. The effects of a whole grain enriched hypocaloric diet on cardiovascular disease risk factors in men and women with metabolic syndrome. ***Am J Clin Nutr*** 2008; 87: 79-90.
20. Koh-Banerjee P, Rimm EB. Whole grain consumption and weight gain: a review of the epidemiological evidence, potential mechanisms and opportunities for future research. ***Proc Nutr Soc*** 2003; 62: 25-29
21. Malhotra A, Maruthappu M, Stephenson T. Healthy eating: an NHS priority A sure way to improve health outcomes for NHS staff and the public. ***Postgrad Med J*** 2014; 90: 671-672.