

# The Effect of Visceral Abdominal Fat Volume on Oxidative Stress and Proinflammatory Cytokines in Subjects with Normal Weight, Overweight and Obesity

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**Purpose:** The increase of visceral abdominal fat (VAF) and oxidative stress (OS) are independent predictors for cardiovascular risk. This study aimed to determine the association of VAF with proinflammatory cytokines, oxidants, antioxidants, and oxidative damage to DNA in subjects with normal weight, overweight, and obesity.

**Patients and Methods:** A cross-sectional study that included 21 men and 71 women who attended for a medical check-up was conducted. Dual-energy X-ray absorptiometry (DXA) was used to measure the VAF volume. ELISA and colorimetric techniques were used for chemical analysis.

**Results:** Low activity of superoxide dismutase (SOD) was found in overweight and obese subjects compared to the normal weight group ( $p=0.005$ ). In contrast, the activity of glutathione peroxidase (GPx) was higher in the overweight and obesity groups compared to the normal weight subjects ( $p=0.017$ ). The total antioxidant capacity (TAC) was also increased in the overweight group compared to the normal weight group ( $p=0.04$ ). According to the volume of VAF, the levels of tumor necrosis factor alpha and interleukin 6 showed no differences between subjects with normal and high VAF. Subjects with high VAF show higher levels of 8-isoprostans compared to normal VAF group ( $p=0.039$ ). Less concentration of 8-oxoguanine-DNA-N-glycosylase-1 (hOGG1) was found in the high VAF group ( $p=0.032$ ) compared to the normal VAF subjects. VAF was positively correlated with lipoperoxides (LPO) ( $r=0.27$ ,  $p<0.05$ ) and 8-isoprostanes ( $r=0.25$ ,  $p<0.05$ ). We also found correlations between oxidative stress markers and anthropometric ratios for intra-abdominal fat. The waist-hip ratio was positively correlated with LPO ( $r=0.30$ ,  $p<0.05$ ) and TAC ( $r=0.24$ ,  $p<0.05$ ).

**Conclusion:** These findings suggest that the predominantly oxidative damage associated with VAF in overweight or obesity is lipoperoxidation and oxidative DNA damage. Alterations in endogenous antioxidant defenses may not be linked to the amount of VAF.

**Keywords:** oxidative stress, oxidative DNA damage, antioxidant enzymes, Lunar iDXA, visceral fat cutoff score

## Introduction

Obesity is a multifactorial disease that involves environmental components linked to unhealthy lifestyles characterized by increased intake of high-energy foods that favor the gradual accumulation of adipose tissue.<sup>1</sup> Obesity determines important repercussions in the appearance of chronic degenerative diseases, which affects the costs of medical care for the population.<sup>2</sup>

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In Mexico, a progressive increase in obesity has been observed since 2000.<sup>2</sup> It was previously reported that 62% of Mexican adults are at least overweight.<sup>3</sup> Adipose tissue is considered an important endocrine organ with high lipid storage capacity for systemic management of energy substrates. Excessive lipid loading produces adipocyte stress with the ability to cause adverse effects on obesity.<sup>4</sup> High accumulation of visceral adipose fat (VAF) leads to visceral obesity and the release of proinflammatory cytokines. In addition, VAF associated with the development of metabolic disorders such as type 2 diabetes mellitus (T2DM), hypertension, cardiovascular disease, and other chronic diseases. Some inaccurate anthropometric measures are used to estimate visceral obesity, such as waist-circumference and waist-hip ratio.<sup>5–7</sup> There are accurate methods to measure VAF, such as magnetic resonance imaging and computed tomography. However, both are expensive and produce prolonged radiation exposure.<sup>8</sup> Dual-energy X-ray absorptiometry (DXA) is a useful imaging technique that offers a simple, fast, and accurate estimate of VAF mass and volume with low radiation exposure.<sup>9</sup>

Oxidative stress (OS) links obesity with its associated complications. Dyslipidemia, low antioxidant defenses, increased proinflammatory molecules, and reactive oxygen species (ROS) favor OS production.<sup>10</sup> ROS can damage the DNA chain. Oxidation of guanine forms 8-hydroxy-2'-deoxyguanosine (8-OH-dG) or 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG).<sup>11</sup> These base oxidations can lead to cellular damage. Guanine bases can be repaired under normal conditions by the enzyme oxo-guanine glycosylase (OGG1).<sup>12</sup>

An increase in lipoperoxidation (LPO), and 8-epi-prostaglandin F2 (8-iso-PGF2 $\alpha$ ) products and their correlation with VAF in patients with metabolic syndrome front non-obese subjects have previously demonstrated.<sup>13–15</sup>

The main antioxidants that neutralize ROS are catalase, superoxide dismutase (SOD) and glutathione peroxidase (GPx).<sup>16,17</sup> Recently, the inverse relationship of SOD enzyme activity with VAF in obese men was reported.<sup>18</sup> However, the clinical behavior of antioxidant enzyme activity concerning VAF has not clarified. The objective of the study was to determine the association of VAF on the endogenous antioxidant activity, oxidative markers, and proinflammatory cytokines in subjects with normal weight, overweight, and obesity.

## Patients and Methods

### Subjects and Anthropometric Measures

Ninety-two adult subjects who attended at the University Clinic of the University Center of Health Sciences of the University of Guadalajara for a medical check-up were included. For each patient was measured height, weight, waist-hip ratio. Body mass index (BMI) calculated as; weight divided by the square of the height (kg/m<sup>2</sup>). Waist circumference was measured between the lower margin of the last palpable rib and the top of the iliac crest. Hip circumference was taken around the widest portion of the buttocks. Then, the waist-hip ratio was calculated.<sup>19</sup> The study subjects were divided according to the criteria of the World Health Organization (WHO) for BMI in normal weight (18.5–24.9 kg/m<sup>2</sup>), overweight (25–29.9 kg/m<sup>2</sup>) and obesity ( $\geq 30$  kg/m<sup>2</sup>).<sup>20</sup>

Subjects with systolic blood pressure  $\geq 130$  mmHg or diastolic blood pressure  $> 80$  mmHg were considered hypertensive.<sup>21</sup> T2DM established as fasting plasma glucose  $\geq 126$  mg/dL.<sup>22</sup> Dyslipidemia was set as high triglycerides ( $\geq 150$  mg/dL), low HDL cholesterol ( $< 40$  mg/dL) or high LDL cholesterol ( $\geq 160$  mg/dL).<sup>23</sup> No maintenance therapy was excluded. Subjects that reported cerebrovascular disease, hepatitis, kidney disease, or those who were taking antioxidants were not included.

For each participant, 10 mL of 8 h fasting blood was taken, 5 mL with EDTA, and 5 mL in the dry tube. The blood sample was centrifuged at 3000 rpm for 10 min at room temperature. The supernatant (serum, plasma) was stored at  $-80^{\circ}\text{C}$  until final processing.

### Visceral Abdominal Fat

The volume of VAF was determined by dual-energy x-ray densitometry (DXA). The densitometer Lunar iDXA, GE Healthcare<sup>®</sup>, Madison, WI with CoreScan<sup>®</sup> (software version 16.0) was used. The subjects lay supine with arms and palms placed parallel to body one centimeter from thigh aligned. The legs were fully extended, taking care that the feet did not touch each other. The scanning and cuts of the regions of interest were adjusted manually according to the manufacturer's instructions. Visceral fat measurement was performed by subtracting subcutaneous adipose tissue from the android fat. The coefficient of variation using a phantom standard was 0.25%. The same expert technician in DXA performed the scans.<sup>24</sup>

## Proinflammatory Cytokines

### TNF- $\alpha$ and IL6

ELISA kit 900-K25 and 900-K16 (Peprotech, Rocky Hill, NJ 08553, USA<sup>®</sup>) were used to determine the TNF- $\alpha$  and IL-6, respectively. Both cytokines had a detection limit of 32 pg/mL. The cytokine identification was made in 100  $\mu$ L of a plasma sample. The plate was read at a wavelength of 405 nm with correction set at 650 nm. The TNF- $\alpha$  intra-assay coefficient of variation (CV) was 2.1%, and IL-6 intra-assay CV was 4.7%.

## Oxidative Stress Markers

### Products of Liperoxidation

The serum LPO was measured by using FR12 assay kit (Oxford Biomedical Research Inc., Oxford, MI, USA<sup>®</sup>). Plasma samples treated with N-methyl-2-phenylindole were centrifuged at 12,791 rpm for 10 min, and the supernatant was obtained. The supernatant was added to a microplate, and absorbance was measured at 586 nm. The duplicate standard intra-assay CV was 6.4%.

### 8-Isoprostane

Plasma samples were analyzed according to the competitive ELISA assay (ABCAM ab175819<sup>®</sup> Cambridge, United Kingdom). A 96 well microplate pre-coated with a capture antibody for 8-Isoprostanes was used. The optical density was read at 450 nm. The duplicate standard intra-assay CV was 4.1%.

### Nitric Oxide (NO)

Before the assay, plasma samples were deproteinized by the addition of zinc sulfate (6 mg of zinc sulfate was added to 400  $\mu$ L of the sample), vortexed for one min and the samples were centrifuged at 10,000-x g for 10 min at 4°C. For measure NO, the kit NB98, Oxford Biochemical, Oxford, MI, USA<sup>®</sup> was used. The colorimetric signal was read at 540 nm. The duplicate standard intra-assay CV was 7.9%.

## Antioxidants

### Superoxide Dismutase

The kit (SOD No. 706002, Cayman Chemical Company<sup>®</sup>, USA). The serum samples were diluted 1:2 in sample buffer before the colorimetric assay. Color development was read at a wavelength of 440 nm. The dilution factor was used to calculate the results. The duplicate standard intra-assay CV was 5.4%.

### Glutathione Peroxidase

It was used the assay kit GPx 703,102 (Cayman Chemical Company<sup>®</sup>, USA). Plasma samples (20  $\mu$ L) were added to a microplate of 96 wells with 70  $\mu$ L of buffer, 50  $\mu$ L of glutathione and glutathione reductase mixture and 50  $\mu$ L of NADPH. The activity was obtained by measuring the absorbance decrease at 340 nm every min for 20 min. The activity expressed as nmol/min/mL. The duplicate of positive control intra-assay CV was 1.5%.

### Catalase

We used the commercial kit Catalase-520 from Bioxytech (OxisResearch<sup>TM</sup><sup>®</sup> Foster City, USA). Erythrocyte lysate was obtained from whole blood collected in EDTA tube centrifuged at 2500 g for 5 min. Erythrocyte lysate was washed three times with cold 0.9% NaCl and diluted 1/400 with deionized water. The colorimetric assay was performed, and coloration was read at 520 nm. The duplicate standard intra-assay CV was 2.3%.

### Total Antioxidant Capacity

Total antioxidant capacity (TAC) quantification was done following the (Total Antioxidant Power Kit, No. TA02.090130, Oxford Biomedical Research<sup>®</sup>). The serum samples and standards were diluted 1:40, and 200  $\mu$ L were placed in each well of a microplate. Concentration was expressed as mM equivalents of Trolox (an analog of vitamin E). The duplicate standard intra-assay CV was 5.7%.

## Oxidative Damage to DNA and Repair

### 8-Hydroxy-2'-Deoxyguanosine

The assay 8-hydroxy-2'-deoxyguanosine No. ab201734 Abcam<sup>®</sup>, Cambridge, United Kingdom, was used. This competitive ELISA assay was performed with 50  $\mu$ L of serum samples. The color signal measured at 450 nm. The duplicate standard intra-assay CV was 6.9%.

### 8-Oxoguanine-DNA-N-Glycosylase-I

We followed ELISA kit hOGG-1 MBS702793 (My BioSource<sup>®</sup>, San Diego, CA). The optical density was read at 450 nm with a correction set at 540 nm using. The duplicate standard intra-assay CV was 11.3%. For every optical density measure, the Synergy<sup>TM</sup> HT multi-detection microplate reader (Bio-Tek, Winooski, VT, USA) was used.

### Statistical Analysis

Anthropometric data were expressed as mean  $\pm$  SD or percentages. OS markers were expressed as mean  $\pm$  SEM. The Kolmogorov-Smirnov test was used to analyze

the normality distribution of data. To analyze the differences between multiple groups for continuous variables, we used one way ANOVA or Kruskal–Wallis test with the post-hoc Dunn–Bonferroni test for pairwise comparison. The inter-group comparison was conducted with Student's *t*-test or Mann–Whitney *U*-test. For categorical variables, the difference between the groups was calculated with Chi<sup>2</sup> test. Spearman correlation test was used to evaluate the relation between the OS markers and the body mass measurements. The cutoff point for VAF was obtained using a receiver operating characteristic (ROC) curve analysis. The sensitivity, specificity, area under the curve (AUC), and confidence interval (CI) were calculated for the components of metabolic disorder (hypertension, dyslipidemia, or T2DM). The score with the highest Youden's index (sensitivity + specificity-1) was considered the optimal cutoff score. Two-tailed  $p \leq 0.05$  was considered statistically significant. SPSS for Windows version 20.0 (IBM SPSS statistics Inc., Chicago, IL, USA) was used.

### Ethical Considerations

The research complies with the ethical principles for medical research in human beings stipulated in the Declaration of Helsinki 64th General Assembly, Fortaleza, Brazil October 2013. In addition to adhering to the standards of Good Clinical Practices. All procedures were performed according to regulations stipulated in the General Health Legal Guidelines for Health Care Research in Mexico, 2nd Title, in Ethical Aspects for Research in Human Beings, Chapter 1, and Article 17. All patients gave and signed the informed consent form in the presence of signed witnesses. The Local Ethics and Research Committee from the Institute of Experimental and Clinical Therapeutics, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara (CEI/487/2019) approved the study.

## Results

### Comparison Between BMI Groups

Subjects included in this study were classified in normal weight, overweight, and obese subjects. The obesity group included all the subjects with  $\geq 30$  kg/m<sup>2</sup>. Twenty-one men with  $56 \pm 13$  years of age and seventy-one women of  $57 \pm 10$  years of age were included. The overall prevalence of dyslipidemia and T2DM was 30% and 16%, respectively. VAF showed a progressive increase in overweight and obese subjects ( $p < 0.01$ ). The waist-hip ratio was higher in the obese subjects compared with normal weight ( $p = 0.01$ ). The prevalence of hypertension was significantly higher in overweight

(28%) and obesity (49%) compared with normal weight ( $p = 0.02$ ). Levels of TNF- $\alpha$  and IL-6 were similar between normal weight, overweight, and obesity. No significant differences were found in oxidants or oxidative damage to DNA. The activity of SOD was significantly decrease in overweight ( $0.35 \pm 0.05$  U/mL) and obese subjects ( $0.34 \pm 0.06$  U/mL) compared to normal weight ( $0.50 \pm 0.04$  U/mL,  $p = 0.005$ ). Contrary, the GPx activity was found increase in overweight ( $2.41 \pm 0.33$  nmol/min/mL) and obese subjects ( $2.17 \pm 0.25$  nmol/min/mL) compare to normal weight ( $1.28 \pm 0.16$  nmol/min/mL,  $p = 0.015$ ). The total antioxidant capacity was also higher in overweight ( $2.34 \pm 0.11$  mM) compared to the normal weight subjects ( $2.19 \pm 0.10$  mM,  $p = 0.05$ ). [Table 1](#)

### Cutoff Score for High Visceral Abdominal Fat

[Table 2](#) shows the results of ROC analysis and the optimal cutoff score for cardio-metabolic risk factors. The VAF volume had the highest AUC for hypertension and the lowest for dyslipidemia. The AUC for hypertension also showed the highest combination of specificity and sensibility with a Youden's index of 0.45. The optimal cutoff score for hypertension was  $1658.50$  cm<sup>3</sup> of VAF.

### Clinical Characteristics Between Normal and High Visceral Abdominal Fat

In [Table 3](#), subjects were divided into normal VAF ( $< 1658.50$  cm<sup>3</sup>) and high VAF ( $\geq 1658.50$  cm<sup>3</sup>). The high VAF subjects showed a significant prevalence of hypertension ( $p < 0.001$ ) and T2DM ( $p = 0.02$ ). No differences in dyslipidemia between normal vs high VAF was found. Contrary to that found in BMI, subjects with high VAF had increased levels of 8-Isoprostane  $30.85 \pm 3.79$  pg/mL vs  $21.70 \pm 1.02$  pg/mL in normal VAF ( $p = 0.039$ ). Decreased concentration of hOGG1  $3.07 \pm 1.15$  ng/mL in high VAF front  $5.81 \pm 0.92$  ng/mL in normal VAF ( $p = 0.032$ ) was found.

### Correlations

The volume of VAF and BMI were correlated proportionately with 8-Isoprostanes ( $r = 0.249$ ,  $p < 0.05$  and  $r = 0.261$ ,  $p < 0.05$ ). The waist-hip index was correlated proportionally with LPO ( $r = 0.274$ ,  $p < 0.05$ ) and with TAC ( $r = 0.244$ ,  $p < 0.05$ ). LPO also was positively correlated with volume of VAF ( $r = 0.274$ ,  $p < 0.05$ ). Age showed positive proportional correlation with 8-OHdG ( $r = 0.278$ ,  $p < 0.05$ ) [Table 4](#).

**Table 1** Demographic Data, Inflammatory Cytokines and Oxidative Status in Subjects with Normal Weight, Overweight and Obesity

	Normal Weight	Overweight	Obesity	P
	n-23	n-36	n-33	
Gender				
Men n (%)	5 (21.7)	7 (19.4)	9 (27.3)	0.73
Women n (%)	18 (78.3)	29 (80.1)	24 (72.7)	
Age years	68.77±10.66	55.03±10.66	56.45±10.84	0.32
Visceral abdominal fat cm <sup>3</sup>	777.09±472.36	1270.92±471.15 <sup>a,b</sup>	1988.59±471.57 <sup>a</sup>	<0.01*
Hypertension n (%)	3 (13)	10 (28)	16 (49)	0.02***
Dyslipidemia n (%)	8 (35)	10 (28)	10 (30)	0.71
T2DM n (%)	3 (13)	5 (14)	7 (21)	0.68
Waist-hip ratio	0.85±0.08	0.88±0.08	0.91±0.06 <sup>a</sup>	0.01*
Inflammatory Cytokines				
TNF- $\alpha$ pg/mL	866.86±153.95	680.97±79.67	694.44±86.06	0.96
IL-6 pg/mL	437.62±78.06	920.09±253.77	566.50±127.31	0.93
Oxidative Damage to DNA and Repair				
8-OHdG ng/mL	43.93±10.12	54.85±16.04	153.32±54.46	0.15
hOGGI ng/mL	5.42±1.58	4.89±1.13	4.97±1.26	0.82
Oxidants				
LPO $\mu$ M	4.30±0.42	3.58±0.23	3.80±0.22	0.18
8-Isoprostane pg/mL	24.25±2.20	20.81±1.22	28.44±3.09	0.27
Nitric oxide $\mu$ M	234.81±11.37	238.28±10.09	242.36±10.12	0.74
Antioxidants				
SOD U/mL	0.50±0.04	0.35±0.05 <sup>a</sup>	0.34±0.06 <sup>a</sup>	0.005**
GPx nmol/min/mL	1.28±0.16	2.41±0.33 <sup>a</sup>	2.17±0.25 <sup>a</sup>	0.015**
Total antioxidant capacity mM	2.19±0.10	2.34 ± 0.11 <sup>a</sup>	2.28 ± 0.09	0.05**
Catalase mU/mL	18.07±2.00	16.75±1.31	18.35±1.72	0.46

**Notes:** Values are mean  $\pm$  SD, SEM, or percentage. <sup>a</sup>vs normal weight. <sup>b</sup>vs obesity. \*\*\*Chi-square test, \*Student's t-test, \*\*Kruskal–Wallis test.

**Abbreviations:** T2DM, type 2 diabetes mellitus; TNF, tumor necrosis factor alpha; IL-6, interleukin 6; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; hOGGI, human oxoguanine glycosylase; LPO, lipoperoxides; SOD, superoxide dismutase; GPx, glutathione peroxidase.

## Discussion

The main findings of the present study show that OS is proportionally correlated with increase VAF volume, waist-hip ratio, and BMI in overweight and obesity. In addition, the activity of antioxidant enzymes was found altered in overweight and obese subjects.

It is estimated that the prevalence of overweight and obesity worldwide increased between 1980 and 2013 by 27.5% for adults and 47.1% for children.<sup>25</sup>

In Mexico, the prevalence of obese or overweight people reported in 2017 was 62%.<sup>3</sup> Some authors showed that prevalence is expected to increase to 88% for men and 91% for women for 2050.<sup>26</sup> In the present study, we found 75% prevalence of overweight and obesity in women and 76% in men. Even though VAF accumulation is associated with cardiovascular risks, there are only a few data related to ranges of normal or high VAF volume. Some studies used computed

**Table 2** Cutoff Points for Visceral Abdominal Fat by Metabolic Disorder Risk Factors

	AUC	95% CI	Cutoff (cm <sup>3</sup> )	Sensitivity	Specificity	YI	p
Hypertension	0.74	0.63; 0.85	1658.50	0.58	0.87	0.45	<0.001*
T2DM	0.67	0.53; 0.82	1730.50	0.53	0.81	0.34	0.034*
Dyslipidemia	0.59	0.48; 0.73	1212.00	0.70	0.53	0.23	0.15

**Note:** \*Significant for receiver operating characteristic (ROC) curve analysis.

**Abbreviations:** T2DM, type 2 diabetes mellitus; AUC, area under the curve; CI, confidence interval; YI, Youden's index.

**Table 3** Clinical Characteristics in Normal and High Visceral Abdominal Fat

	Normal VAF (<1658.5 cm <sup>3</sup> )	High VAF (≥1658.5 cm <sup>3</sup> )	p
Age years	55.97±10.70	58.96±9.60	0.30
Gender			
Men n (%)	11 (16.7)	10 (38.5)	0.025***
Women n (%)	55 (83.3)	16 (61.5)	
BMI kg/m <sup>2</sup>	26.89±3.83	33.50±5.45	<0.001*
Waits-hip ratio	0.87±0.08	0.92±0.52	0.003*
Hypertension n (%)	12 (18.2)	18 (69.2)	<0.001***
Dyslipidemia n (%)	19 (28.8)	10 (38.5)	0.39
T2DM n (%)	7 (10.6)	8 (30.8)	0.020***
Inflammatory Cytokines			
TNF-α pg/mL	775.07±80.36	656.11±55.62	0.90
IL-6 pg/mL	595.06±122.85	864.45±227.39	0.75
Oxidative Damage to DNA and Repair			
8-OHdG ng/mL	67.92±16.45	137.07±61.79	0.39
hOGGI ng/mL	5.81±0.92	3.07±1.15	0.032**
Oxidants			
LPO μM	3.84 ± 0.21	3.90±0.22	0.34
8-Isoprostane pg/mL	21.70±1.02	30.85±3.79	0.039**
Nitric oxide μM	234.67±7.58	250.87±8.84	0.42
Antioxidants			
SOD U/mL	0.36±0.03	0.42±0.07	0.75
GPx nmol/min/mL	2.06±0.23	2.09±0.18	0.23
Total antioxidant capacity mM	2.27±0.07	2.31±0.13	0.75
Catalase mU/mL	18.06±1.10	17.26±1.73	0.89

**Notes:** Values are mean ± SD, SEM or percentage. \*\*\*Chi-square test, \*Student's t-test, \*\*Mann Whitney U-test.

**Abbreviations:** VAF, visceral abdominal fat; BMI, body mass index; T2DM, type 2 diabetes Mellitus; TNF, tumor necrosis factor alpha; IL-6, interleukin 6; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; hOGGI, human oxoguanin glycosylase; LPO, Lipoperoxides; SOD, Superoxide dismutase; GPx, Glutathione peroxidase.

**Table 4** Correlation Between the Visceral Abdominal Fat and Markers of Oxidative Stress in Overweight and Obesity

	Age	VAF	WHR	BMI
LPO	0.072	0.274*	0.302*	-0.185
Total antioxidant capacity	-0.008	-0.020	0.244*	0.092
8-OHdG	0.278*	-0.042	0.239	0.024
8-isoprostanes	0.041	0.249*	0.085	0.261*

**Notes:** Correlation was done using Spearman correlation test. \*p<0.05.

**Abbreviations:** LPO, lipoperoxides; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; VAF, visceral abdominal fat; WHR, waits-hip ratio; BMI, body mass index.

tomography to settle cutoff points of VAF in the Japanese population.<sup>27,28</sup>

More recently, different cutoff scores of VAF were established for men (≥599 cm<sup>3</sup>) and women (≥399 cm<sup>3</sup>) as a predictor for systolic blood pressure ≥130 mmHg in healthy young European population using DEXA method.<sup>29</sup> In our study, VAF volume values differ from those reported in

Japanese and European populations. In the available literature, we did not find previously standardized values of VAF in the world or Mexican population apart from those reported in the European and Japanese population. The prevalence of BMI ≥30 kg/m<sup>2</sup> reported for Japanese (3.5%) and European (36.5%) people compared to Mexico may be the main reason for the differences in these findings.<sup>30,31</sup>

Lipid peroxidation is a process by which oxidants such as free radicals or non-radical species attack lipids with carbon-carbon double bonds. Malondialdehyde (MDA) is the main product of LPO. It is associated with increasing high levels of cholesterol and hypertension.<sup>32,33</sup> It has been shown that MDA increases in obese patients compared to healthy people.<sup>34,35</sup> In the present study, the levels of LPO among subjects with normal weight, overweight, and obesity were similar. This result could be related to the fact that dyslipidemia was homogeneously distributed between groups. Dyslipidemia is characterized by high

serum levels of total and LDL cholesterol, and they positively correlate with LPO levels in obesity.<sup>36</sup> Therefore, one might expect to find similar levels of MDA among the three groups studied because the prevalence of dyslipidemia was also similar. Abbasian et al reported a positive correlation between MDA with BMI and waist circumference.<sup>33</sup> Xiao et al showed a positive correlation between LPO with BMI and VAF.<sup>18</sup> Our findings add confirmation to the correlation of LPO between the volume of VAF and waist-hip ratio. 8-Isoprostanes can also represent the OS.

8-Isoprostanes is a family derived from the oxidation of arachidonic acid. 8-Isoprostanes can be measured in urine, serum, plasma, and other biological fluids and tissues.<sup>37,38</sup> 8-Isoprostanes are increased in obesity compared to healthy non-obese controls.<sup>39</sup> There is evidence that 8-Isoprostanes correlate negatively with HDL-C cholesterol.<sup>40</sup> Urinary 8-Iso-PGF<sub>2α</sub> is positively correlated to BMI and VAF area in obese subjects with or without metabolic syndrome.<sup>18,41</sup>

However, Sjogren et al found no correlation of 8-Iso-PGF<sub>2α</sub> with BMI.<sup>42</sup> Our results showed no differences in levels of 8-Isoprostanes between subjects of normal weight, overweight, and obesity. Contrary, we found a correlation between serum 8-Isoprostane and BMI. Subjects with high VAF volume showed an elevated concentration of 8-Isoprostane than normal VAF. In addition, 8-Isoprostane was positively correlated to VAF volume. These findings suggest that the OS represented by the serum concentration of LPO and 8-Isoprostanes is related to the accumulation of VAF.

NO is a free radical and has vasodilatory, anti-thrombotic, anti-proliferative, and anti-inflammatory effects in the vasculature.<sup>43</sup> Under OS, NO reacts with the radical O<sub>2</sub><sup>•-</sup> to generate peroxynitrite (ONOO<sup>-</sup>), causing damage to the endothelium.<sup>44</sup> Controversial data is reported about NO behavior in obesity. NO is associated with increasing BMI, and it is related to metabolic disorders.<sup>45,46</sup> Some studies report that NO decreases in obesity.<sup>47</sup> Our study found no differences in NO levels between normal weight, overweight, obesity, or high VAF. Similar results were reported by other authors who found no statistical differences in NO levels in obesity.<sup>48,49</sup> Furthermore, it is described that the capacity of the endothelium to release NO under basal conditions is not compromised in overweight and obese adults.<sup>50</sup>

Adipocytes secrete TNF-α and IL-6, and their concentration is associated with the percentage and distribution of

adipose tissue in the body. These cytokines are critical in the mechanisms for the induction of persistent inflammatory state production in obese subjects.<sup>51</sup> In our study, we found similar levels of these two cytokines in subjects with normal weight, overweight, obesity, or high VAF. These data reflect similar sub-clinical inflammatory status within the subjects included in the study.

The oxidative DNA damage marker was increased in overweight and was higher in obesity almost three times (NS). It has been reported that obese people have DNA damage. Tursi Rísoli et al, showed a significant increase in the marker of oxidative damage to DNA in obese patients compared to those of normal weight. However, it is essential to consider that the BMI reported by the author, was higher than that found in our study.<sup>52</sup> Oxidative damage to DNA has mutagenic potential. Previous studies described the high concentration of oxidative DNA damage was related to obesity and tumorigenesis. These studies suggest that patients with high BMI have a significant risk of carcinogenesis.<sup>53,54</sup>

The existence of the DNA repair system is essential to overcome the damage and maintain the integrity of the DNA structure. There is reported that the induction of ROS in human cells participates in the inhibition of DNA repair by increasing protein oxidation.<sup>55</sup> The hOGG1 enzyme is one of the most critical oxidative enzymes that repair DNA damage. The deficiency of this enzyme developed metabolic disorders such as low glucose tolerance, higher insulin levels, and liver steatosis.<sup>56</sup> In our study, DNA repair enzyme levels were slightly lower in overweight and obese subjects than in normal-weight subjects (NS). Nevertheless, a significant decrease was found in high VAF volume subjects. These findings could mean that VAF is a better indicator of oxidative DNA damage than BMI.

Antioxidant defense enzymes have been described in obesity. Furukawa et al show that mRNA expression of SOD, GPx, and catalase is reduced in obese-induced rats,<sup>41</sup> whereas Vincent et al reported the opposite, an increase of these enzymes, also in a rat model.<sup>57</sup>

It has been previously reported that the activity of the antioxidant enzymes SOD, GPx, and catalase was reduced in obese children, adolescents, and adult women. There was even a negative correlation between SOD and GPx enzymes with BMI.<sup>58,59</sup> However, another study did not report statistical differences in SOD, GPx, and catalase between high BMI (>24 kg/m<sup>2</sup>) and low BMI (<24 kg/m<sup>2</sup>).<sup>60</sup> Also, an increase in TAC levels was previously reported in

**Table 5** Antioxidants Between Normal Weight vs Comorbidities Normal Weight, Overweight and Obese Subjects

	Normal Weight (n 11)	Comorbidities Normal Weight (n 12)	Overweight (n 36)	Obese (n 33)	p
SOD U/mL	0.45 ± 0.05	0.54 ± 0.06	0.35 ± 0.05 <sup>a,b</sup>	0.34 ± 0.06 <sup>a,b</sup>	0.01*
GPx nmol/min/mL	0.80 ± 0.15 <sup>b</sup>	1.67 ± 0.21 <sup>a</sup>	2.41 ± 0.33 <sup>a,b</sup>	2.17 ± 0.25 <sup>a,b</sup>	0.003*

**Notes:** Values are mean ± SEM. Table 5 The table shows only the significant values between subjects of normal weight and normal weight with comorbidities. \*Kruskal-Wallis test. <sup>a</sup>vs normal weight, <sup>b</sup>vs comorbidities normal weight.

**Abbreviations:** SOD, superoxide dismutase; GPx, glutathione peroxidase;

overweight and obese subjects compared to the normal weight group.<sup>61</sup>

In the present study, we found a significant decrease in SOD activity and an increase in GPx in overweight and obese subjects compared to the normal weight group. We found a significant increase in TAC in overweight subjects compared to those of normal weight.

Our normal weight group includes subjects with T2DM, hypertension, and dyslipidemia. Therefore, we made a subgroup of normal weight without comorbidities (Table 5). We still found significant differences in the activity of SOD and GPx in overweight and obese subjects, compared with normal weight with or without comorbidities. However, Brown et al reported no differences in SOD activity and glutathione concentration in healthy normal weight and overweight and obese subjects.<sup>62</sup>

Some demographic characteristics may be linked to these different findings. An animal model study indicates that the increase in age may decrease the expression of Gpx.<sup>63</sup> Gender characteristics could be another influential factor. However, in this study, both the value of age and the frequency of gender were distributed homogeneously among the normal weight, overweight, and obesity groups ( $p=0.32$ ,  $p=0.73$ , respectively). This distribution helps to discard these variables as confounding factors for this study.

The mayor clinical evidence available about the association between fat distribution, including VAF, and OS focus on markers of oxidative damage and its effects on mitochondrial activity processes.<sup>13,14,64</sup> Little is the evidence related to antioxidant defenses. Heval et al reports that glutathione concentration correlates inversely with the amount of various fat deposits, such as gynoid fat, android fat, and total fat.<sup>65</sup> Xiao et al reported that SOD correlated negatively with the VAF area.<sup>18</sup> Nevertheless, we found no correlation between enzymatic antioxidants and VAF volume. Our findings indicate that the increase of VAF is associated with OS represented as an increase in oxidants markers, mostly lipoperoxidation. Besides, the activity of

antioxidant enzymes may not have a significant role in this association.

Strengths. As far as we know, this is the first study that gives exploratory cutoff values of VAF volume for cardio-metabolic risks as hypertension, T2DM, and dyslipidemia in the Mexican population. However, an improved cutoff of VAF volume for risk assessment is needed. As mentioned before, the available literature reviewed in this study reports that the association between OS and VAF is limited to lipoperoxidation markers. Accordingly, information related to other types of oxidative damage and the behavior of antioxidant defenses is still lacking. This study shows broader characteristics of the oxidative state with high VAF, which can help identify the specific OS mechanisms associated with VAF presented since overweight and obesity. This data could lead to the design of new longitudinal studies with a diagnostic or therapeutic approach.

Limitations of the study. A cross-sectional study was conducted with a limited number of subjects, and no causality between VAF and blood indicators can establish from this study design. The subjects included were predominantly women (77%) and some men who spontaneously attended a medical review. The cutoff values for VAF volume were exploratory and obtained from the Mexican population by using the densitometer Lunar iDXA, GE Healthcare<sup>®</sup>, and, therefore, may not be suitable to compare with other populations or methods. We emphasize that subjects with normal weight, overweight, and obesity were not healthy, they have hypertension, dyslipidemia, or T2DM, and these associated pathologies are capable of altering the results of the metabolites analyzed.

## Conclusion

The OS markers LPO and 8-isoprostanes are correlated with VAF in obese or overweight subjects. Besides, subjects with high VAF show decreased hOGG1 concentration and a tendency to increased 8-OHdG. The activity of



endogenous antioxidant enzymes (SOD, GPx) showed changes in overweight or obese subjects. However, these changes did not show to be associated with VAF. These findings suggest that the predominantly oxidative damage associated with VAF in overweight or obesity is lipoperoxidation and oxidative DNA damage. Further prospective studies are needed to establish the causality of VAF on OS.

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The authors declare that they have no conflicts of interest.

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