Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Association of Biomarkers for Dyslipidemia, Inflammation, and Oxidative Stress with Endothelial Dysfunction in Obese Youths: A Case–Control Study

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Objective: The United Arab Emirates (UAE), with its characteristic local population, geography, and history, presents several risk factors for cardiovascular diseases (CVDs) in obese individuals. Obesity and its associated complications, including diabetes, atherogenic dyslipidemia, and CVDs leading to significant health risks. In the present study, "Youths" defined as young people between 18 and 22 years. We assessed dyslipidemia, inflammation, and oxidative stress biomarker levels and their association with endothelial dysfunction (ED) in both overweight/obese and normal weight youths of UAE.

Methods: There were 160 youths with overweight/obese (BMI $\geq$ 25 kg/m^2) patients and healthy age- and sex-matched normal weight (BMI $\leq$ 24.9 kg/m^2) as controls participated in this study. The anthropometric data and blood samples were collected to assess the biomarkers for dyslipidemia, inflammation, oxidative stress, ED from all the youths.

Results: The overall mean age and male-to-female ratio were 20±1.5years and 1.0:1.2, respectively. There was statistically significant difference in HDL-C ($p<0.001$), triglycerides (TG) ($p<0.001$), ApoA ($p=0.002$), ApoB/ApoA ratio ($p=0.009$) between the overweight/obese and normal weight youths. Among, inflammatory markers: hs-CRP, IL-6, TNF-α also showed significant $p<0.001$ and oxidative stress markers: DNA/RNA Damage, catalase and nitric oxide (NO) showed significant $p<0.001$ between groups. Spearman correlation of ED markers with lipid profile markers showed Vitamin C levels positively correlated with HDL-C ($p<0.001$) and negatively correlated with glucose ($p<0.001$). ICAM-1showed significant negative correlation with HDL-C ($p<0.01$) and ApoA ($p<0.001$) but positive correlation with TG ($p<0.01$) and HbA1c ($p<0.001$) among groups. Spearman correlation of ED markers with inflammatory/oxidative stress biomarkers showed Vitamin C levels negatively correlated with ferritin ($p < 0.001$), NO ($p < 0.001$), GGT ($p < 0.001$), and ALT ($p < 0.001$) levels. The ICAM-1showed significant positive correlation with hs-CRP ($p < 0.01$), IL-6 ($p < 0.001$), TNF-α ($p < 0.01$), GGT ($p < 0.05$), and ALT ($p < 0.05$) in both groups.

Conclusion: This study revealed a strong link between the biomarkers of dyslipidemia, inflammation, and oxidative stress with ED in overweight/obese patients. This study might be used to predict future cardiovascular events in this population.

Keywords: dyslipidemia, inflammation, oxidative stress, endothelial dysfunction, obesity, youth

Introduction

The United Arab Emirates (UAE) and the whole region of the Middle east (ME) are classified as high- and middle-income countries. They have gone through rapid social transformation from rural to urban lifestyle in the last 7 to 8 decades. Coronary artery disease (CAD) occurs at younger age in the ME than all other parts of the world. In the UAE, with its unique local population, geography, and history; numerous risk factors contribute to the development of cardiovascular diseases (CVDs) in obese patients.[1]

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Obesity is defined as excessive fat deposition that can interfere with the normal metabolic processes. It is a chronic condition associated with various metabolic syndromes, with a rapidly increasing prevalence in children, youths, and adults.[2] Endothelial dysfunction (ED), inflammation, and oxidative stress are early interrelated factors in CVD etiology.[3] Interventions for cardiovascular complications of obesity have proven beneficial in delaying and decreasing the increased risk of morbidity and mortality. Furthermore, targeting controllable factors that contribute most significantly to the global CVD burden, including tobacco use, hypertension, and secondary prevention of CVD, can affect the greatest mortality reduction.[4] Atherosclerosis is a complex, continuous, multifactorial disease, the earliest stages of which occur in early childhood.[5,6] The disease is characterized by a long asymptomatic but progressive initial phase, which is subsequently accelerated by the presence of various risk factors, such as a family history of CAD, dyslipidemia, obesity, hypertension, and diabetes mellitus.[6,7] Arterial ED is the earliest sign of atherogenesis and is a marker of arterial damage, followed by intima-media thickening, which precedes plaque formation.[8] Endothelial dysfunction is associated with obesity, hyperlipidemia, diabetes mellitus, and cigarette smoking in teenagers and young adults.[9] Oxidative stress occurs when the generation of reactive oxygen species (ROS) surpasses the scavenging capacity of antioxidants, which may be mediated by a genetic lack in the synthesis of antioxidant enzymes and environmental triggers like viral infections.[10] This is predominantly due to the decreased bioavailability of nitric oxide (NO) in the vessel walls.[3]

Rising rates of obesity and its complications, such as diabetes mellitus, atherogenic dyslipidemia, and CVD (such as stroke and ischemic heart disease), pose serious health concerns among youths of UAE. There is growing evidence that functional impairment of the endothelium is one of the first recognizable signs of atherosclerosis development and is present long before the occurrence of CVD. Therefore, understanding the endothelium's central role provides not only insights into pathophysiology but also a possible clinical opportunity to detect early disease, stratify cardiovascular risk, and assess response to treatments.[3,11,12] Youths are especially vulnerable to the complications of these disorders and are generally less engaged in health-promoting and monitoring programs. So, measures designed to study this youth population to prevent and treat obesity and its associated complications are vital. Therefore, the purpose of this study was to examine the association between the biomarkers for dyslipidemia, inflammation, and oxidative stress with endothelial dysfunctions in obese UAE national youths.

Methods

Participants

Asymptomatic youths (18–22 years of age) age- and sex-matched with body mass index (BMI $\geq$ 25kg/m^2) were in overweight/obese group and normal weight youths had BMI:18–24.9 kg/m^2. Seventy-four overweight/obese youth were matched with age- and gender normal weight (n=86) youth from UAE University. As per the clinical guidelines we used to define youths from 18 to 22 years of age.[13–16] The exclusion criteria include any medical illness, family history of premature CVD, stability in the previous year, and regular medications or vitamin supplementation.

Sample Size

Using the Lachin[17] formula, the powerSurvEpi R package was implemented, we conducted a post hoc power analysis.[18] With 74 sets, a 1:1 overweight/obese (patients): normal weight (control) ratio, a two-side 5% significance level (α), coefficient of determination (R^2) estimated as the square of the correlation coefficient of ICAM-1 and HDL-C and standard deviation of ICAM-1 retrieved from the literature.[19] Using these parameters and estimates, our study had 80% power to detect an odds ratio (OR) of 1.007 associated with one unit change in ICAM-1 in overweight/obese compared to normal youth.

Anthropometric Measurements

A trained research nurse used simple questionnaire to ask about personal history of smoking, and family history of hypertension, diabetes mellitus, and heart attack plus the parental consanguineous marriage. The research nurse performed all the measurements, including anthropometric measurements. Waist circumference was measured using the upstretched midpoint of the tape from the bottom of the rib cage to the tip of the iliac crest. The neck circumference was measured using

the tape around the neck. Blood pressure (BP) and pulse was measured using a calibrated Omron M6 IntelliSense (Healthcare, Kyoto, Japan) automatic BP monitor, and the sleeves were suitable for each arm size. The weight of the youths was recorded to the nearest 0.1kg on digital scales in light clothing, and the height was measured to the nearest 0.1cm in a standing position without shoes. The body fat composition and electrical impedance or BF% were measured by electrical impedance using the Tanita Body composition analyzer TANITA TBF-300, maeno-cho, Tokyo, Japan.

Blood Collection

Blood samples were collected in tubes containing potassium EDTA and anticoagulant, thoroughly mixed at room temperature, and transferred to the laboratory. Both plasma and serum tubes were stored at −80°C after centrifugation at 4000 rpm for 10 min.

Dyslipidemia Biomarkers

Total cholesterol, HDL-C, LDL-C, TG, LPA, Oxi LPA, OxPAPC, apolipoprotein A (Apo-A), apolipoprotein B (Apo-B), glucose, and HbA1C were measured using specialized ELISA kits.

Inflammatory Biomarkers

Cytokines and soluble receptors [interleukin- IL-6, TNF-α,]; hs-CRP, ferritin, folate, and Vit B12 were evaluated using specialized ELISA kits.

Oxidative Stress Biomarkers

Oxidative DNA/RNA damage, NO, superoxide dismutase (SOD), catalase, GGT, and alanine aminotransferase.

Endothelial Dysfunction Biomarkers

Soluble adhesion molecules ICAM-1, sVCAM-1, and vitamin C were analyzed in the plasma samples.

Ethics

This study was approved by Al Ain Medical District Human Research Ethics committee (AAMDHREC) (ERH-2020-6058 2020–01). The study was conducted in accordance with the Declaration to Helsinki and following the institutional ethical committee's review. Informed consents were obtained from all the participants in this study.

Statistical Analysis

Categorical variables were presented using frequencies and percentages, while continuous variables were summarized using mean (SD) or median (Q25, Q75) if normality assumption was not satisfied. The Chi-square or Fisher's exact test were used to compare the proportions for categorical variables, and the Two sample *t*-test or Wilcoxon rank sum test were used to compare means or ranks for continuous variables. Spearman's rho rank correlations were utilized to evaluate the relationships between various parameters and biomarkers among overweight/obese patients and normal weight controls. An adjusted conditional logistic regression model was employed to examine the associations between overweight/obesity and various biomarkers, while accounting for the matched variables of age and gender. The model for each biomarker was adjusted for systolic blood pressure, as well as for family history of hypertension and diabetes mellitus. All P values were 2-sided and $p < 0.05$ was considered statistically significant. All analyses were conducted using R (version 4.2.2).

Results

Participants' Characteristics

In this study, 160 participants with mean ± SD as 20±1.5 years and a small majority of female (54%) were enrolled (Table 1). Almost half (46%) of youths were either overweight or obese. The average weight and height were 72 kg (SD: 22 kg) and 165 cm (SD:10cm), respectively, with median waist circumference of 79 cm (IQR: 68–92 cm) and median BF % as 16% (IQR=10–25%). The average systolic and diastolic blood pressures of the youths were 115 mmHg (SD:11

Table 1 Anthropometric and Clinical Variables Among Youths

Variable	Overall N = 160[#]	Overweight/obese N = 74[#]	Normal Weight N = 86[#]	p-value*
Age (years)	20.09 (1.52)	20.18 (1.61)	20.02 (1.44)	0.500
Gender				0.400
Female	86 (54%)	37 (50%)	49 (57%)	
Male	74 (46%)	37 (50%)	37 (43%)	
Smoking				0.500
No	150 (94%)	71 (96%)	79 (93%)	
Yes	9 (5.7%)	3 (4.1%)	6 (7.1%)	
SBP (mmHg)	115 (11)	118 (10)	112 (10)	<0.001
DBP (mmHg)	70.6 (6.2)	72.1 (6.0)	69.4 (6.1)	0.005
Pulse (per min.)	81 (11)	80 (13)	81 (9)	0.500
Height (cm)	165 (10)	167 (10)	164 (10)	0.032
Weight (kg)	72 (22)	88 (21)	58 (9)	<0.001
Body Fat (kg)	25 (10)	33 (8)	18 (6)	<0.001
Body fat (%)	16 (10, 25)	25 (21, 35)	11 (8, 13)	<0.001
Waist Circumference (cm)	79(68, 92)	90(77, 105)	69 (63, 84)	<0.001
Neck Circumference (cm)	33.0(29.4,36.0)	35.0(32.0, 37.0)	32.2(28.0,34.0)	<0.001
Height/Waist Ratio	0.48(0.43,0.54)	0.54(0.48,0.60)	0.44(0.40,0.48)	<0.001
BMI (kg/m^2)	25 (21, 29)	30 (27, 33)	21 (20, 23)	<0.001
Consanguinity	61 (38%)	29 (39%)	32 (37%)	0.800
Family history HTN	66 (41%)	34 (46%)	32 (37%)	0.300
Family history DM	57 (36%)	29 (39%)	28 (33%)	0.400
Family history Heart attack	7 (4.4%)	6 (8.1%)	1 (1.2%)	0.050
Personal history Smoking	29 (18%)	11 (15%)	18 (21%)	0.300

Notes: [#]Mean (SD); Median (IQR); n (%).* Two Sample *t*-test; Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

Abbreviations: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HTN, Hypertension; DM, diabetes mellitus.

mmHg) and 70.6 mmHg (SD: 6.2 mmHg), respectively, and the average pulse rate was 81 bpm (SD:11 bpm). Among the youths 38% had parenteral consanguinity. The family history of hypertension was 41%, diabetes mellitus 36%, heart attack 4.4%, and smoking 18%. On average, overweight/obese youths had significantly elevated clinical and anthropometric measurements, except for pulse rate compared to normal weight group ($p<0.05$).

Dyslipidemia, Inflammatory, Oxidative Stress, and Endothelial Dysfunction Biomarkers

The HDL-C levels were 47 mg/dL and 57 mg/dL ($p<0.001$) and Apo A as 1.37 g/L and 1.47 g/L ($p=0.002$) levels were significantly lower among overweight/obese participants than those of normal weight youths (Table 2). The TG levels were significantly higher in the overweight/obese compared to normal weight youths (106 mg/dL and 65 mg/dL, $p<0.001$). Moreover, all the assessed inflammatory biomarkers (except B12, which showed no association, and folate, which was

Table 2 Lipid Profile, Inflammatory, Oxidative Stress, and Endothelial Dysfunction Biomarker Levels Among Youths

Variable	Overall N = 160[#]	Overweight/obese N = 74[#]	Normal Weight N = 86[#]	p-value*
Lipid profile				
Total Cholesterol (mg\dl)	166 (30)	167 (29)	165 (31)	0.700
HDL-C (mg\dl)	52 (15)	47 (12)	57 (15)	<0.001
LDL-C (mg\dl)	107 (30)	109 (30)	105 (29)	0.300
Triglycerides (mg\dl)	81 (58, 120)	106 (75, 141)	65 (48, 100)	<0.001
LPA (nmol/L)	36 (18, 70)	38 (23, 69)	34 (14, 69)	0.300
Oxi LPA (µg/L)	189 (131, 219)	195 (128, 219)	183 (136, 213)	0.700
OxPAPC	26.5 (5.1)	26.2 (5.7)	26.8 (4.4)	0.500
Apo A (g/L)	1.42 (0.22)	1.37 (0.20)	1.47 (0.22)	0.002
Apo B (g/L)	0.83 (0.24)	0.86 (0.25)	0.81 (0.22)	0.140
ApoB/ApoA ratio	0.60 (0.22)	0.65 (0.24)	0.56 (0.19)	0.009
Glucose (mg\dl)	88 (17)	90 (18)	87 (15)	0.200
HbA1C %	5.03 (0.51)	5.08 (0.60)	4.99 (0.41)	0.300
Inflammatory Biomarkers				
hs-CRP (mg/L)	0.94 (0.33, 2.16)	1.49 (0.77, 3.47)	0.54 (0.27, 1.27)	<0.001
IL-6 (pg/mL)	1.64 (1.06, 2.69)	2.04 (1.58, 4.00)	1.38 (0.99, 1.82)	<0.001
TNF-α (pg/mL)	2.62 (2.10, 4.14)	3.69 (2.52, 5.54)	2.29 (1.98, 3.05)	<0.001
Ferritin (pg/mL)	44 (17, 93)	71 (19, 100)	31 (14, 72)	0.023
Folate (ng/mL)	12.2 (3.5)	11.4 (2.8)	12.8 (3.8)	0.023
Vit B12 (pg/mL)	361 (276, 470)	360 (277, 499)	362 (277, 443)	0.500
Oxidative stress Biomarkers				
DNA/RNA Damage (pg/mL)	39 (10)	47 (9)	32 (5)	<0.001
Catalase (nmol/min/mL)	44 (17)	60 (11)	31 (7)	<0.001
SOD (U/ML)	5.20 (1.39)	4.91 (1.19)	5.45 (1.50)	0.015
NO (µMol/L)	13.1 (12.2, 16.3)	14.9 (12.3, 17.4)	12.5 (12.1, 14.0)	<0.001
GGT (U/L)	18 (14, 24)	18 (15, 26)	17 (14, 22)	0.140
ALT (U/L)	13 (11, 20)	16 (12, 25)	13 (10, 17)	0.026
Endothelial Dysfunction Biomarkers				
Vitamin C (µg/mL)	3.62 (2.34, 4.94)	3.58 (2.16, 4.66)	3.70 (2.62, 5.55)	0.300
ICAM-1 (ng/mL)	212 (173, 254)	234 (195, 268)	191 (166, 232)	<0.001
VCAM-1 (ng/mL)	674 (625, 769)	679 (650, 770)	667 (608, 759)	0.400

Notes: [#]Mean (SD); Median (IQR); n (%).* Two Sample *t*-test; Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

Abbreviations: Apo A, Apolipoprotein A; Apo B, Apolipoprotein B; ALT, Alanine Aminotransferase; GGT, Gamma Glutamyl Transferase; HbA1c, Hemoglobin A1C; hs-CRP, high-sensitivity C-reactive protein; HDL-C, High-density lipoprotein-C; IL-6, Interleukin-6; ICAM-1, Intercellular Adhesion Molecule-1; LDL: Low Density Lipoprotein; NO: nitric oxide; SOD: Superoxide dismutase; TNF-α, Tumor Necrosis Factor alpha; VCAM-1, Vascular Cell Adhesion Molecule-1; oxPAPC, oxidized phospholipid 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine; Vit B12, Vitamin B12.

significantly higher in the normal weight youths) including hs-CRP, IL-6, TNF-α, and ferritin were significantly higher in the overweight/obese participants than those in the normal weights ($p<0.05$). The levels of oxidative stress biomarkers-oxidative DNA/RNA damage, catalase enzyme activity, NO, and ALT were significantly higher in overweight/obese participants than those in normal weight youths ($p<0.05$), and SOD was significantly higher in normal weight participants than in overweight/obese youth (Table 2, Figure 1). ICAM-1 was the only ED biomarker that was significantly associated with BMI status, which was higher in the overweight/obesity group than normal weight group (234 vs 191ng/mL $p<0.001$).

The biomarkers with significant differences from the univariate analysis were entered into multivariable conditional logistic regression analysis adjusted for SBP and family history of HTN and DM (Figure 2). There was a significant negative association between HDL-C (adjusted Odds Ratio (aOR): 0.91, 95% CI: 0.87–0.95; $p < 0.001$) and Apo A (0.03, 95% CI: 0.00–0.22; $p<0.001$) with overweight/obesity. In contrast, TG (1.02, 95% CI: 1.0–1.03; $p<0.001$), and Apo B/Apo A ratio (11.52, 95% CI: 1.66–79.9; $p = 0.013$) were positively associated with overweight/obesity. Increasing ICAM-1 one ng/mL increases the odds of overweight/obesity and 1%. Interestingly, ferritin and NO become non-significant after adjustment for the confounders (Figure 2).

Correlation Between ED Biomarkers with Dyslipidemia, Inflammatory and Oxidative Stress Biomarkers

Although mild positive correlations were observed between HDL-C, OxiLPA, OxPAPC, and folate and vitamin C in both normal and overweight/obese youths, these correlations were stronger in the overweight/obesity group, except for folate in which the correlation was stronger with the normal weight youths (Tables 3 and 4). In contrast, vitamin C was negatively correlated with the TGs, glucose, ferritin, SOD, NO, GGT, and ALT levels in both BMI categories. TGs,

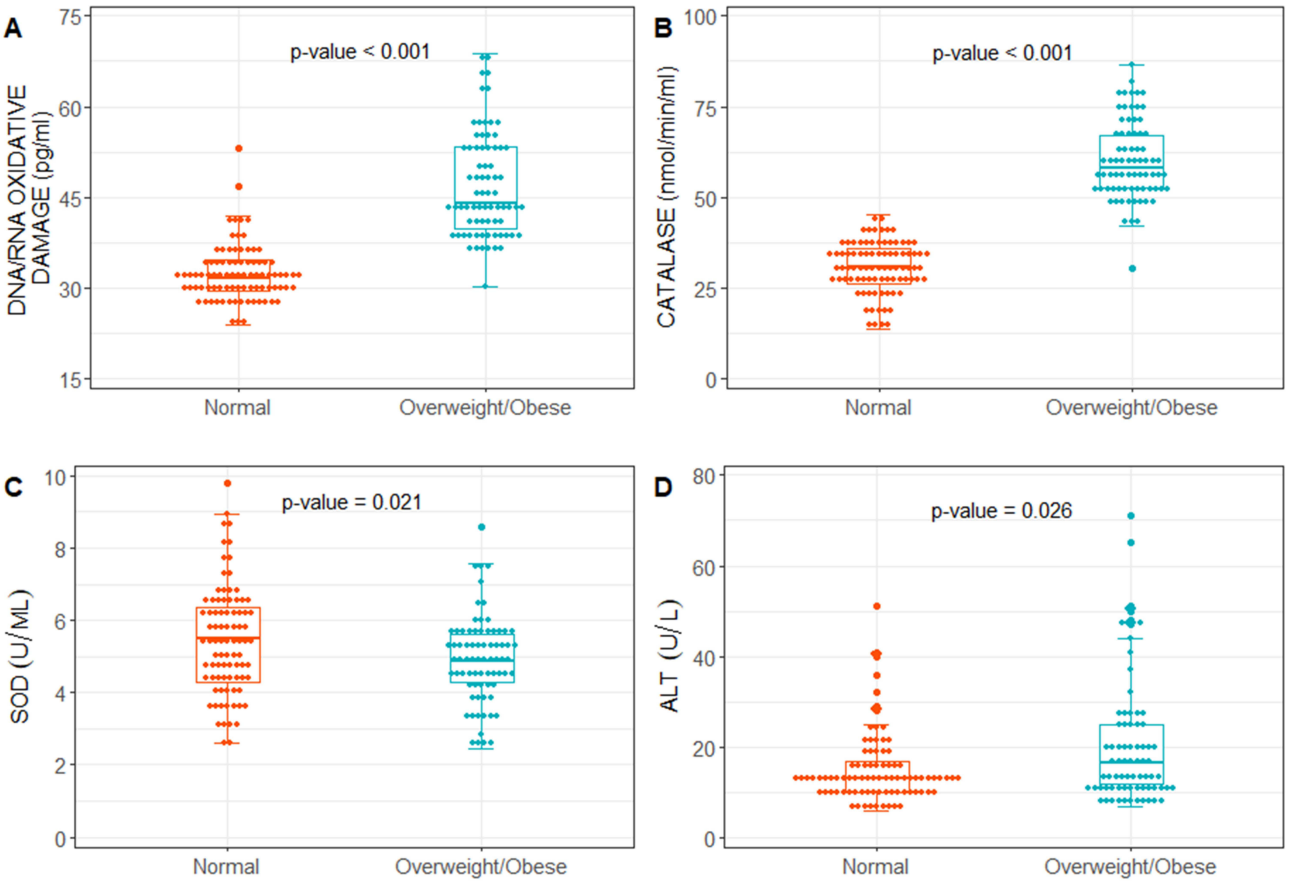

Figure 1 Distribution of (**A**) DNA/RNA oxidative damage (pg/mL), (**B**) Catalase (nmol/min/mL), (**C**) Superoxide dismutases (SODs) (U/ML) and (**D**) Alanine Aminotransferase (ALT) (U/L) among youths.

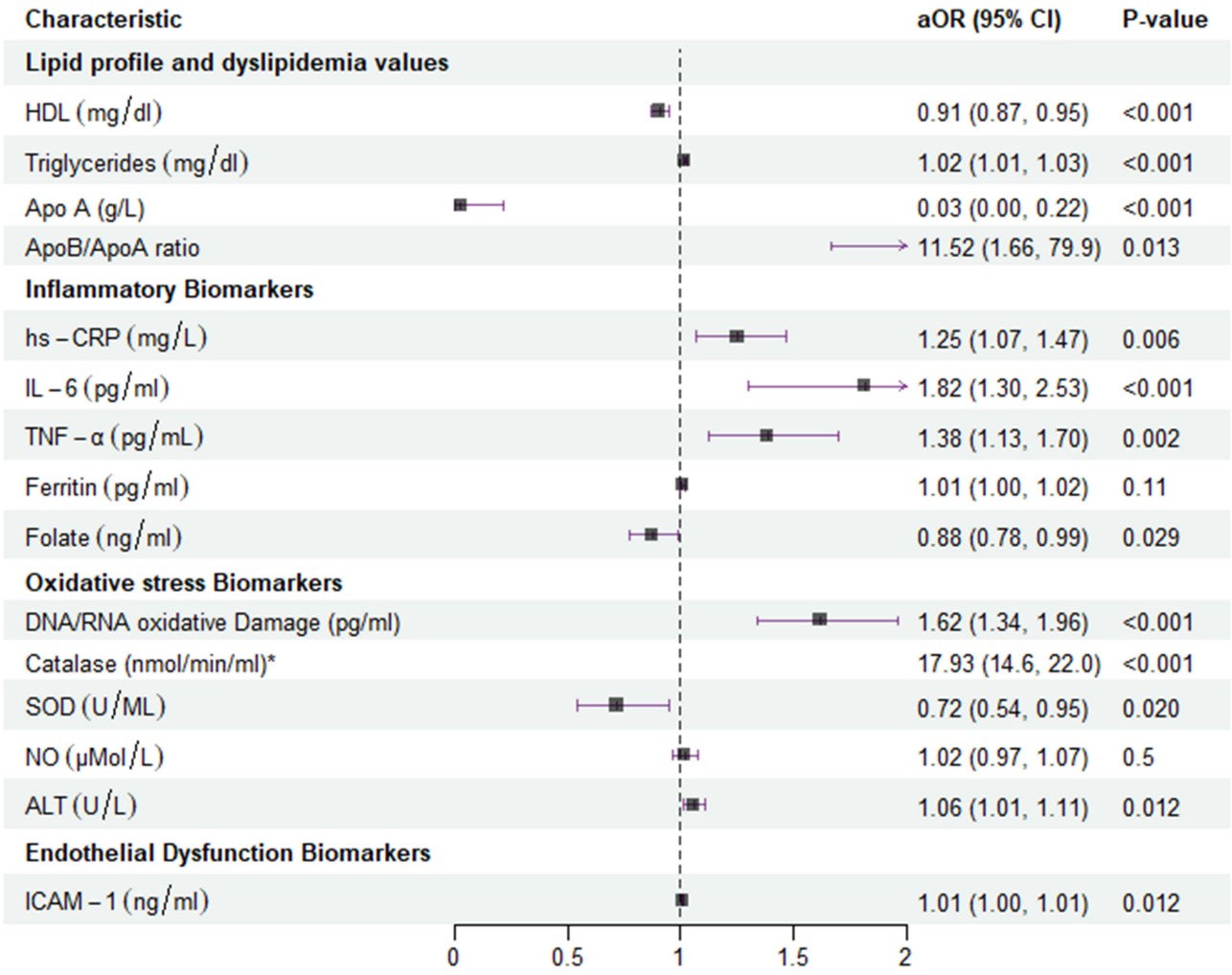

Figure 2 Adjusted conditional logistic regression analysis of the association between overweight/obesity and different determinants.

HbA1c, hs-CRP, IL-6, TNF-α, GGT, and ALT were positively correlated with ICAM-1 within both BMI categories with the overweight/obesity group exhibiting slightly stronger correlations. In contrast, HDL-C, Apo A, and oxidative DNA/RNA damage were negatively correlated with ICAM-1 levels in both groups. Although ICAM-1 and catalase activity

Table 3 Spearman's Rank Correlation Between Endothelial Dysfunction Biomarkers and Lipid Profiles Between Overweight/Obese and Normal Weight Youths

Lipid Profile Biomarkers		Endothelial Dysfunction Biomarkers		
		Vitamin C	ICAM-1	VCAM-1
Total Cholesterol	Overweight/obese	−0.025	0.348	0.167
	Normal	−0.065	0.032	−0.042
HDL-C	Overweight/obese	0.351***	−0.228**	−0.094
	Normal	0.264***	−0.045**	0.141

(*Continued*)

Table 3 (Continued).

Lipid Profile Biomarkers		Endothelial Dysfunction Biomarkers		
		Vitamin C	ICAM-1	VCAM-1
LDL-C	Overweight/obese	−0.017	0.382	0.184
	Normal	−0.047	−0.033	−0.102
Triglycerides	Overweight/obese	−0.215*	0.118**	0.054
	Normal	−0.149*	0.095**	0.063
LPA	Overweight/obese	−0.214	−0.046	−0.113
	Normal	0.075	0.119	0.058
Oxi LPA	Overweight/obese	0.416**	0.090	−0.117
	Normal	0.167**	0.010	0.173
OxPAPC	Overweight/obese	0.376*	0.014	0.089
	Normal	0.012*	0.065	0.105
Apo A	Overweight/obese	−0.015	−0.275***	−0.173
	Normal	0.093	−0.157***	0.063
Apo B	Overweight/obese	−0.190	0.256	0.096
	Normal	−0.114	−0.079	−0.178
ApoA/Apo B	Normal	−0.176	0.326*	0.101
	Overweight/obese	−0.165	−0.005*	−0.161
Glucose	Overweight/obese	−0.271**	0.083	−0.078
	Normal	−0.298**	0.042	0.308
HbA1C	Overweight/obese	0.029	0.336***	0.127*
	Normal	−0.079	0.176***	0.204*

Notes: *p<0.05, **p<0.01, ***p<0.001.
Abbreviations: Apo A, Apolipoprotein A; Apo B, Apolipoprotein B; HbA1c, Hemoglobin A1C; ICAM-1, Intercellular Adhesion Molecule-1; LDL, Low Density Lipoprotein; LPA, lysophosphatidic acid; oxi LPA, oxidized lysophosphatidic acid; VCAM-1, Vascular Cell Adhesion Molecule-1; oxPAPC, oxidized phospholipid 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine.

Table 4 Spearman's Rank Correlation Between Different Endothelial Dysfunction Biomarkers with Inflammatory and Oxidative Stress Biomarkers Among Overweight/Obese and Normal Weight Youths

Inflammatory Biomarkers		Endothelial Dysfunction Biomarkers		
		Vitamin C	ICAM-1	VCAM-1
hs-CRP	Overweight/obese	−0.127	0.173**	−0.001
	Normal	0.020	0.159**	−0.079
IL-6	Overweight/obese	−0.172	0.443***	0.138
	Normal	0.046	0.232***	0.064

(*Continued*)

Table 4 (Continued).

Inflammatory Biomarkers		Endothelial Dysfunction Biomarkers		
		Vitamin C	ICAM-1	VCAM-1
TNF-α	Overweight/obese	−0.156	0.278**	0.187
	Normal	0.073	0.016**	0.091
Ferritin	Overweight/obese	−0.383***	0.051	−0.075
	Normal	−0.288***	0.096	−0.064
Folate	Overweight/obese	0.114*	−0.238	−0.121
	Normal	0.199*	−0.053	−0.139
Vit B12	Overweight/obese	−0.175	−0.199	−0.026
	Normal	−0.090	0.076	0.042
Oxidative stress biomarkers				
DNA/RNA oxidative damage	Overweight/obese	0.213	−0.018*	−0.103
	Normal	0.145	−0.151*	−0.186
Catalase	Overweight/obese	−0.094	0.011**	−0.046
	Normal	0.295	−0.001**	0.023
SOD	Overweight/obese	−0.289*	−0.138	−0.132
	Normal	−0.207*	0.101	0.092
NO	Overweight/obese	−0.581***	−0.132	−0.022
	Normal	−0.288***	0.074	0.075
GGT	Overweight/obese	−0.551***	0.233*	−0.032
	Normal	−0.315***	0.092*	−0.199
ALT	Overweight/obese	−0.500***	0.174*	0.116
	Normal	−0.328***	0.169*	−0.146

Notes: *p<0.05, **p<0.01, ***p<0.001.
Abbreviations: ALT, Alanine Aminotransferase; GGT, Gamma Glutamyl Transferase; hs-CRP, high-sensitivity C-reactive protein; IL-6, Interleukin-6; ICAM-1, Intercellular Adhesion Molecule-1; NO, nitric oxide; SOD, Superoxide dismutase; VCAM-1, Vascular Cell Adhesion Molecule-1; Vit B12, Vitamin B12.

were positively correlated in the overweight/obesity group (r = 0.011, p<0.01), this correlation was negative in the normal weight youths (r = −0.001, p<0.01). The HbA1c was positively correlated with VCAM-1 in both BMI categories, with normal weight youths showing a stronger correlation (r = 0.204 vs 0.127).

Discussion

This study showed the association among ED, dyslipidemia, inflammation, and oxidative stress in obese youths in the UAE. Youths with excess body fat are at a higher risk of systemic inflammation, dyslipidemia, ED, and diabetes. These findings suggest that metabolic biomarkers should be routinely assessed in overweight youths.

Obesity is the world's major cause of comorbidities in diseases such as diabetes mellitus, CVD, various cancers, metabolic syndrome, and other health issues, which can increase morbidity and mortality.[20–23] Obesity and dyslipidemia harm cardiovascular health in adolescents and young adults with diabetes mellitus in the UAE. The risk of atherosclerotic

cardiovascular disease (ACD), including IHD and stroke, is well established in dyslipidemia. Studies on the adult population of UAE have shown high dyslipidemia rates,[24] however, limited data are available on youths. Subclinical inflammation and ED have been reported among young persons with T1DM, which can be CVD predictors.[25] Excess fat in schoolchildren increases their risk of developing systemic inflammation, dyslipidemia, ED, cholestasis, and diabetes.[26]

According to a large cohort study, the relative risk of CVD mortality due to excess weight was higher in young adults than that in older adults.[27] The mean age of the youths in the present study, even 20.09±1.52 years are at risk of various CVD. Studies have shown correlation between a high BMI and ED in various populations, including children,[28] adolescents,[29] Asians,[22] and persons with suspected coronary artery disease.[30] The current study found a substantial disparity in BMI between the overweight/obese and normal weight youths ($p<0.001$).

Research has demonstrated a significant association between childhood obesity and various factors such as body fat composition, lipid profile, inflammation, and ED biomarkers in the UAE population.[31] In the present study, we also observed a significant difference between BF (%) and BF (kg) ($p<0.001$).

Mezhal et al[32] also reported the co-occurrence of obesity and dyslipidemia with other cardiometabolic risk factors such as hypertension and diabetes. In the present study, dyslipidemia diagnosis was associated with older age, higher BMI, and a history of diabetes, hypertension, and CVD. The link between obesity and dyslipidemia is well established.[33] Obesity and inflammatory cytokines, such as TNF-α, and IL-6, are correlated.[34,35] Elevated IL-6 levels in individuals with high BMI serve as a valuable indicator of the correlation between IL-6 levels and the progression of systemic inflammation. Obesity is associated with inflammation and negative alterations in metabolic parameters in both adolescents and young adults in the African-American populations. Furthermore, this study demonstrated that obese African-American adolescents exhibited obesity-related inflammation levels that were comparable to those in adults, as indicated by hs-CRP.[36] In this study, we identified a notable disparity in multiple inflammatory biomarkers between the normal weight and overweight/obese groups. The hs-CRP levels were significantly different ($p<0.001$), as were the IL-6 ($p<0.001$) and TNF-α ($p<0.001$) levels, between the normal weight and overweight/obese youths.

TNF-α plays a role in the body's widespread inflammatory response. It has also been associated with the development of insulin resistance, obesity, and diabetes. TNF-α stimulates NF-κB activation, which promotes an increase in adhesion molecules on endothelial and vascular smooth muscle cell surfaces. This process causes an inflammatory state in the adipose tissue, ED, and eventually, atherosclerosis.[37] In the current study, TNF-α levels between the normal weight and overweight/obese youths were notably different.

Ferritin serves as an indicator of inflammation, rather than iron levels, in overweight or obese individuals. A recent study reported a positive correlation between elevated ferritin levels and metabolic syndrome and obesity risks.[38] Ferritin was positively correlated with hs-CRP and BMI, indicating that ferritin serves as an indicator of inflammation rather than iron status in overweight or obese individuals.[39] The results of our study are consistent with those findings. Serum ferritin exhibits an inverse relationship with vitamin C. Vitamin C is a protective factor, whereas ferritin is a risk factor for hepatic steatosis and fibrosis. The systemically administered high-dose vitamin C is known to restore the endogenous antioxidant potential and improve NO-dependent vasodilatation in the forearm vasculature.[40]

Vitamin C relieves non-alcoholic fatty liver disease (NAFLD) and regulates iron balance by suppressing ferritin and inducing labile iron pool. Studies have shown that elevated ferritin levels pose an NAFLD risk and increased vitamin C protects against NAFLD. In the present study, Vit C levels were significantly negatively correlated with ferritin levels. The SOD, NO, GGT, and ALT levels showed significant negative correlation with Vitamin C levels.

Obesity is a risk factor for an increased likelihood of cardiovascular events. To investigate the possible mechanisms linking obesity to ED, weight loss could be an effective strategy for enhancing endothelial function. Several studies have examined the correlation between lifestyle interventions aimed at reducing weight and improving endothelial function.

Endothelial dysfunction is an initial step in the pathogenesis and development of atherosclerosis.[41] Evidence suggests that obesity induces ED.[42] Consequently, considerable focus has been directed towards understanding the mechanisms that contribute to ED resulting from obesity, with the aim of preventing and treating cardiovascular events. It is characterized by increased contraction and reduced relaxation of the endothelium. Endothelial function is commonly recognized to be compromised in individuals with coronary risk factors. Evidence suggests that ED is a reliable indicator of cardiovascular events.[30] Inflammation, an imbalance between vasodilators and vasoconstrictors, endogenous

endothelial NO synthase (eNOS) uncoupling, and low shear stress are all important mechanisms that contribute to ED.[41] In the present study, we found that ED markers, such as vitamin C, ICAM-1, and VCAM-1 were elevated among overweight/obese youths. We also observed significant differences among various oxidative stress biomarkers, such as oxidative DNA/RNA damage, catalase, SOD, NO, and ALT. The DNA/RNA damage was significantly negatively correlated with ICAM-1 expression in both groups. The elevated serum levels of ALT and GGT are known to be independent markers of the activation of systemic inflammation and increased oxidative stress. These markers are known to have independent relationship to metabolic syndrome, and in occurrence of obesity along with elevated liver enzymes may additively worsen the atherogenic state.[43] In the present study, we observed significant differences in ALT levels between the two groups. ALT and GGT also showed significant positive correlation with ED marker: ICAM-1.

It has been reported that ICAM-1, sVCAM-1, and vitamin C as biomarkers of ED. ICAMs are transmembrane proteins that promote ED and leukocyte migration. The activated endothelial cells produce soluble types of these adhesion molecules that are secreted into the bloodstream. Many studies have reported increased circulating levels of VCAM-1 and/or ICAM-1 associated with CAD, CAD severity and complications.[44]

NO is a physiological regulator of many functions in the cardiovascular, neuromuscular, neurological, genitourinary, gastrointestinal, and renal systems. Inhibitors of NO synthase (INO) reduce NO production and prevent the decrease in insulin secretion caused by free fatty acids. Endothelium-dependent vasodilation of NO is impaired in overweight and obese individuals, and this is also observed during hypercholesterolemia.[45] In obesity and high blood pressure, superoxide and endothelial NO production may increase peroxynitrite levels, decrease NO availability, and cause liver vasoconstriction.[46] In this study, we observed a significant difference in NO levels between groups. The oxidative DNA/RNA damage and catalase: Cat Activity showed a significant negative correlation with the ED marker, ICAM-1, among the groups.

Thus, ED is the first step in the process of atherogenesis and earliest quantifiable functional abnormality of the vessel wall. It is significantly and closely related to the occurrence of cardiac events, which worsen as ED increases. Among overweight/obese patients' and related disorders, such as type 2 diabetes mellitus endothelial injury is characterized by impaired endothelium-dependent vasodilation and increased vasoconstrictor activity.[47]

The treatment of obesity often improves or even normalizes obesity associated insulin resistance or hypertension, and doing so also improves ED. Recently, ED itself became a therapeutic target. There is an option for therapeutic issues for ED in those with CVD risk factors as primary and secondary endothelial therapy. The function and underlying signaling pathway of oxidative stress, dyslipidemia and inflammatory factors in endothelial dysfunction, with the introduction of recent therapeutic targets for the treatment of cardiovascular diseases.[48] The measurement and treatment of ED may become soon part of assessment and stratification of CVD risk factors especially in young patients.

Conclusion

This study revealed a strong link between the biomarkers of dyslipidemia, inflammation, and oxidative stress with endothelial dysfunction in overweight/obese patients. The endothelial dysfunction biomarkers showed strong positive correlation with TGs, HbA1c, IL-6 and negative correlation with HDL-C, Apo A, ferritin, NO, and SOD. This would enable us to predict future cardiovascular events in this population. A larger prospective study may provide further evidence on mechanistic link between cardiometabolic risk factors and future cardiovascular events.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Gehani AA, Al-Hinai AT, Zubaid M, et al. Association of risk factors with acute myocardial infarction in Middle Eastern countries: the INTERHEART Middle East study. *Eur J Prev Cardiol*. 2014;21(4):400–410. doi:10.1177/2047487312465525
2. Schwalm JD, McKee M, Huffman MD, Yusuf S. Resource effective strategies to prevent and treat cardiovascular disease. *Circulation*. 2016;133(8):742–755. doi:10.1161/CIRCULATIONAHA.115.008721
3. Park KH, Park WJ. Endothelial dysfunction: clinical implications in cardiovascular disease and therapeutic approaches. *J Korean Med Sci*. 2015;30(9):1213–1225. doi:10.3346/jkms.2015.30.9.1213
4. Kopelman PG. Obesity as a medical problem. *Nature*. 2000;404(6778):635–643. doi:10.1038/35007508
5. Berenson GS, Srinivasan SR, Bao W, Newman WP, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa heart study. *N Engl J Med*. 1998;338(23):1650–1656. doi:10.1056/NEJM199806043382302
6. Tounian P, Aggoun Y, Dubern B, et al. Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children: a prospective study. *Lancet*. 2001;358(9291):1400–1404. doi:10.1016/S0140-6736(01)06525-4
7. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. *Circulation*. 2010;122(25):e584–636. doi:10.1161/CIR.0b013e3182051b4c
8. Celermajer DS. Endothelial dysfunction: does it matter? Is it reversible? *J Am Coll Cardiol*. 1997;30(2):325–333. doi:10.1016/S0735-1097(97)00189-7
9. Järvisalo MJ, Putto-Laurila A, Jartti L, et al. Carotid artery intima-media thickness in children with type 1 diabetes. *Diabetes*. 2002;51(2):493–498. doi:10.2337/diabetes.51.2.493
10. Sochett E, Noone D, Grattan M, et al. Relationship between serum inflammatory markers and vascular function in a cohort of adolescents with type 1 diabetes. *Cytokine*. 2017;99:233–239. doi:10.1016/j.cyto.2017.07.013
11. Sincer I, Gunes Y, Mansiroglu AK, Cosgun M, Aktas G. Association of mean platelet volume and red blood cell distribution width with coronary collateral development in stable coronary artery disease. *Interv Cardiol*. 2018;14(3):263–269. doi:10.5114/aic.2018.78329
12. Li X, Yu C, Liu X, et al. A prediction model based on systemic immune-inflammatory index combined with other predictors for major adverse cardiovascular events in acute myocardial infarction patients. *J Inflamm Res*. 2024;17:1211–1225. doi:10.2147/JIR.S443153
13. Omar KA, Omar D, Othman S, Yusoff ZM. Reviewing youth facility requirements for low-cost housing in Malaysia. *Procedia Soc Behav Sci*. 2016;222:702–709. doi:10.1016/j.sbspro.2016.05.231
14. Available from: https://www.who.int/southeastasia/health-topics/adolescent-health. Accessed June 13, 2024.
15. Rumain B, Schneiderman M, Geliebter A. Prevalence of COVID-19 in adolescents and youth compared with older adults in states experiencing surges. *PLoS One*. 2021;16(3):e0242587. doi:10.1371/journal.pone.0242587
16. Clinical Guidelines on the Identification. Evaluation, and treatment of overweight and obesity in adults--the evidence report. national institutes of health. *Obes Res*. 1998;6(Suppl 2):51s–209s.
17. Lachin JM. Sample size evaluation for a multiply matched case-control study using the score test from a conditional logistic (discrete Cox PH) regression model. *Stat Med*. 2008;27(14):2509–2523. doi:10.1002/sim.3057
18. powerSurvEpi: power and sample size calculation for survival analysis of epidemiological studies CRAN - Package powersurvepi. Comprehensive R Archive Network; 2021. Available from: https://cran.r-project.org/web/packages/powerSurvEpi/index.html. Accessed June 13, 2024.
19. Lee HA, Choi EJ, Park B, et al. The association between metabolic components and markers of inflammatory and endothelial dysfunction in adolescents, based on the Ewha Birth and growth cohort study. *PLoS One*. 2020;15(5):e0233469. doi:10.1371/journal.pone.0233469
20. Fernández-Sánchez A, Madrigal-Santillán E, Bautista M, et al. Inflammation, oxidative stress, and obesity. *Int J Mol Sci*. 2011;12(5):3117–3132. doi:10.3390/ijms12053117
21. Skinner AC, Perrin EM, Moss LA, Skelton JA. Cardiometabolic risks and severity of obesity in children and young adults. *N Engl J Med*. 2015;373(14):1307–1317. doi:10.1056/NEJMoa1502821
22. Kajikawa M, Maruhashi T, Kishimoto S, et al. Association of body mass index with endothelial function in Asian men. *Int J Cardiol*. 2021;324:186–192. doi:10.1016/j.ijcard.2020.09.029
23. Field AE, Coakley EH, Must A, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch Intern Med*. 2001;161(13):1581–1586. doi:10.1001/archinte.161.13.1581
24. Ibrahim M, Nabil S. Dyslipidaemia prevalence and associated risk factors in the United Arab Emirates: a population-based study. *BMJ Open*. 2019;9(11):e031969. doi:10.1136/bmjopen-2019-031969
25. Aburawi EH, AlKaabi J, Zoubeidi T, et al. Subclinical Inflammation and endothelial dysfunction in young patients with diabetes: a study from United Arab Emirates. *PLoS One*. 2016;11(7):e0159808. doi:10.1371/journal.pone.0159808
26. Aburawi EH, Al Hamad S, Yasin J, Almekhaini LA, Souid AK. Dyslipidemia, subclinical inflammation, hepatic cholestasis and endothelial dysfunction in schoolchildren with excess fat: a study from the United Arab Emirates. *PLoS One*. 2019;14(1):e0210316. doi:10.1371/journal.pone.0210316
27. Stevens J, Cai J, Pamuk ER, Williamson DF, Thun MJ, Wood JL. The effect of age on the association between body-mass index and mortality. *N Engl J Med*. 1998;338(1):1–7. doi:10.1056/NEJM199801013380101
28. Peña AS, Wiltshire E, MacKenzie K, et al. Vascular endothelial and smooth muscle function relates to body mass index and glucose in obese and nonobese children. *J Clin Endocrinol Metab*. 2006;91(11):4467–4471. doi:10.1210/jc.2006-0863
29. Pareyn A, Allegaert K, Verhamme P, Vinckx J, Casteels K. Impaired endothelial function in adolescents with overweight or obesity measured by peripheral artery tonometry. *Pediatr Diabetes*. 2015;16(2):98–103. doi:10.1111/pedi.12139
30. Morimoto H, Kajikawa M, Oda N, et al. Endothelial function assessed by automatic measurement of enclosed zone flow-mediated vasodilation using an oscillometric method is an independent predictor of cardiovascular events. *J Am Heart Assoc*. 2016;5(12). doi:10.1161/JAHA.116.004385
31. Yasin J, Sharma C, Hashim MJ, Al Hamed S, AlKaabi J, Aburawi EH. Cross-sectional association between body fat composition and biomarkers of inflammation and endothelial dysfunction in children with overweight/obesity. *Diabetes Metab Syndr Obes*. 2023;16:483–493. doi:10.2147/DMSO.S390071

32. Mezhal F, Oulhaj A, Abdulle A, et al. The interrelationship and accumulation of cardiometabolic risk factors amongst young adults in the United Arab Emirates: the UAE healthy future study. *Diabetol Metab Syndr*. 2021;13(1):140. doi:10.1186/s13098-021-00758-w
33. Vekic J, Zeljkovic A, Stefanovic A, Jelic-Ivanovic Z, Spasojevic-Kalimanovska V. Obesity and dyslipidemia. *Metabolism*. 2019;92:71–81. doi:10.1016/j.metabol.2018.11.005
34. Rasouli N, Kern PA. Adipocytokines and the metabolic complications of obesity. *J Clin Endocrinol Metab*. 2008;93(11 Suppl 1):S64–73. doi:10.1210/jc.2008-1613
35. Cao H. Adipocytokines in obesity and metabolic disease. *J Endocrinol*. 2014;220(2):T47–59. doi:10.1530/JOE-13-0339
36. DeLoach S, Keith SW, Gidding SS, Falkner B. Obesity associated inflammation in African American adolescents and adults. *Am J Med Sci*. 2014;347(5):357–363. doi:10.1097/MAJ.0b013e31829555f0
37. Lastra G, Manrique CM, Hayden MR. The role of beta-cell dysfunction in the cardiometabolic syndrome. *J Cardiometab Syndr*. 2006;1(1):41–46. doi:10.1111/j.0197-3118.2006.05458.x
38. Gillum RF. Association of serum ferritin and indices of body fat distribution and obesity in Mexican American men--the third national health and nutrition examination survey. *Int J Obes Relat Metab Disord*. 2001;25(5):639–645. doi:10.1038/sj.ijo.0801561
39. Khan A, Khan WM, Ayub M, Humayun M, Haroon M. Ferritin is a marker of inflammation rather than iron deficiency in overweight and obese people. *J Obes*. 2016;2016:1937320. doi:10.1155/2016/1937320
40. Aschauer S, Gouya G, Klickovic U, et al. Effect of systemic high dose vitamin C therapy on forearm blood flow reactivity during endotoxemia in healthy human subjects. *Vascul Pharmacol*. 2014;61(1):25–29. doi:10.1016/j.vph.2014.01.007
41. Higashi Y, Noma K, Yoshizumi M, Kihara Y. Endothelial function and oxidative stress in cardiovascular diseases. *Circ J*. 2009;73(3):411–418. doi:10.1253/circj.CJ-08-1102
42. Koenen M, Hill MA, Cohen P, Sowers JR. Obesity, adipose tissue and vascular dysfunction. *Circ Res*. 2021;128(7):951–968. doi:10.1161/CIRCRESAHA.121.318093
43. Yamada J, Tomiyama H, Yambe M, et al. Elevated serum levels of alanine aminotransferase and gamma glutamyltransferase are markers of inflammation and oxidative stress independent of the metabolic syndrome. *Atherosclerosis*. 2006;189(1):198–205. doi:10.1016/j.atherosclerosis.2005.11.036
44. Constans J, Conri C. Circulating markers of endothelial function in cardiovascular disease. *Clin Chim Acta*. 2006;368(1–2):33–47. doi:10.1016/j.cca.2005.12.030
45. DeSouza CA, Van Guilder GP, Greiner JJ, Smith DT, Hoetzer GL, Stauffer BL. Basal endothelial nitric oxide release is preserved in overweight and obese adults. *Obes Res*. 2005;13(8):1303–1306. doi:10.1038/oby.2005.157
46. Dobrian AD, Schriver SD, Lynch T, Prewitt RL. Effect of salt on hypertension and oxidative stress in a rat model of diet-induced obesity. *Am J Physiol Renal Physiol*. 2003;285(4):F619–628. doi:10.1152/ajprenal.00388.2002
47. Barton M. Childhood obesity: a life-long health risk. *Acta Pharmacol Sin*. 2012;33(2):189–193. doi:10.1038/aps.2011.204
48. Huynh DTN, Heo KS. Therapeutic targets for endothelial dysfunction in vascular diseases. *Arch Pharm Res*. 2019;42(10):848–861. doi:10.1007/s12272-019-01180-7