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Research article

Association of low-grade inflammation and oxidative stress with metabolic dysfunction in healthy obese individuals

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Abstract: Obesity has emerged as a global epidemic and is a major risk factor for various chronic conditions, including insulin resistance, type 2 diabetes, and cardiovascular diseases. We aimed to investigate the validity of soluble suppression of tumorigenicity 2 (sST2), high sensitivity c-reactive protein (hs-CRP), malondialdehyde (MDA), and 8-hydroxy-2-deoxyguanosine (8-OHdG) as potential biomarkers for low-grade inflammation and oxidative stress in obese individuals. Moreover, to explore their association with metabolic dysfunctions. A recruited cohort of 90 subjects of both genders were categorized as obese (BMI BMI > 30 kg/m^2). In addition to the glycemic and lipid profile, a panel of inflammatory (sST2 and hs-CRP) and oxidative stress biomarkers (DMA and 8-OHdG) were assessed using ELISA. Body Mass Index (BMI) and the mean diastolic blood pressure (DBP) were significantly higher in the obese subjects than in controls ($p = 0.0001$ and 0.03, respectively). Fasting blood sugar (FBS) and triglyceride (TG) were significantly higher in the study group ($p = 0.01$ and 0.001) compared to the control group. LDL showed substantial elevation in obese subjects ($p = 0.001$), but HDL was remarkably reduced ($p = 0.02$). The hs-CRP and sST2 levels were significantly elevated ($p = 0.001$) in obese individuals, and both MDA and 8-OHdG indicated a similar pattern ($p = 0.001$ and 0.000). BMI exhibited a positive correlation with all assessed inflammatory and oxidative stress biomarkers. In contrast, FBS and triglyceride (TG) demonstrated a significant association with hs-CRP, 8-OHdG, and MDA, but not with sST2. Furthermore, LDL, VLDL, and LDL/HDL showed a statistically significant positive correlation with hs-CRP and MDA. The elevated levels of all mediators were closely associated with metabolic dysfunction, emphasizing the interplay between obesity and low-grade chronic inflammation. This also highlights the potential for increased cardiovascular risk over time.

Keywords: obesity; low-grade inflammation; oxidative stress; metabolic dysfunction; cardiovascular risk; sST2; 8-OHdG; MDA; hs-CRP

1. Introduction

Metabolic diseases are a spectrum of metabolic dysregulation affecting glucose homeostasis, lipid metabolism, and the pro-inflammatory immune response, including obesity, hyperlipidemia, and non-alcoholic fatty liver disease (NAFLD) [1]. Obesity, among the aforementioned diseases, is a public health concern nowadays. It is defined by the World Health Organization (WHO) as excess accumulation of visceral fat due to an imbalance in energy intake compared to expenditure. It is associated with various alterations in hormonal, biological, and endothelial levels [2].

The worldwide prevalence of obesity has dramatically increased over the past 50 years, reaching pandemic levels that could be due to the reduced quality of the global food system and the sedentary lifestyle. The prevalence varies significantly among countries influenced by cultural norms, socioeconomic status, and local environments [3]. For instance, obesity rates are higher among people with better economic status in developing countries [4]. Obesity is associated with reduced quality of life and lower productivity, such as osteoarthritis, a common consequence of obesity and the leading cause of disability and early retirement [5]. Approximately 2.1 billion adults are categorized as overweight or obese globally, with 1.5 billion individuals as overweight and more than 650 million adults identified as obese. This escalating obesity epidemic has assumed alarming extents, posing considerable risks not only to individual health outcomes but also to broader social well-being [6].

The etiology of obesity is complex and multifactorial, involving genetic, environmental, and societal factors. Obesity substantially increases the risk of various diseases, including type 2 diabetes, cardiovascular diseases (such as myocardial infarction, hypertension, and stroke), musculoskeletal disorders, depression, and certain types of cancer such as breast, ovarian, and colorectal cancer [7]. Considered a risk factor for a variety of diseases, the World Obesity Federation and the American Medical Associations have declared obesity as a chronic progressive disease [8].

Low-grade chronic inflammation is a persistent, low-level inflammatory response due to the continuous activation of the immune system without an acute inflammatory response, and is often associated with metabolic disorders and aging. Studies have shown that overweight or obese individuals exhibit altered serum levels of inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), interleukins (IL-6 and IL-18), and resistin [9]. The elevated levels are linked to a higher risk of chronic diseases such as type 2 diabetes, cardiovascular diseases, chronic kidney disease, and cancer. Furthermore, 50% of all deaths worldwide are directly or indirectly linked to the progression of inflammatory-related diseases [10]. Oxidative stress refers to an imbalance between the production of reactive oxygen species (ROS) and the body's capacity to detoxify these reactive intermediates or repair the resultant damage. This imbalance can result in cellular injury and has been implicated in the pathogenesis of a variety of diseases [11].

In obesity, the adipose tissue becomes inflamed due to increased macrophage infiltration. This results in elevated levels of inflammatory markers and oxidative stress due to increased fatty acid release and subsequent lipid peroxidation [12]. Mitochondria are a significant source of ROS during normal metabolism. Chronic inflammation can exacerbate mitochondrial dysfunction, increasing oxidative stress that further perpetuates inflammatory immune cascade. Moreover, it can impair

endothelial function through oxidative damage that promotes vascular permeability and platelet aggregation, contributing to cardiovascular disease risk [13]. Therefore, various interventions that aim to reduce body weight are essential in improving low-grade inflammation and metabolic abnormalities in obese individuals. Dietary intervention, specifically caloric restriction, has been proven effective in reducing inflammation in obesity and related metabolic dysfunctions [14]. Furthermore, regular exercise is crucial for improving chronic inflammation and obesity-related conditions such as metabolic syndrome since it has proven effective in reducing metabolic hormones [15]. Concerning pharmacological interventions, GLP-1 agonist medications have consistently demonstrated improved cardiovascular outcomes among populations with diabetes [16].

Preclinical and clinical studies show that low-grade chronic inflammation in the adipose tissues is associated with organ compilations and metabolic diseases in obese people [17]. Despite this well-documented paradigm, numerous immunological aspects concerning the precise mechanistic involvement of inflammation in obesity should be evaluated. Here, we aim to investigate the validity of a panel of inflammatory and oxidative stress biomarkers as potential markers for low-grade chronic inflammation and oxidative damage, including high soluble suppression of tumorigenicity-2 (sST2), high-sensitivity C-reactive protein (hs-CRP), malondialdehyde (MDA), and 8-hydroxy-2-deoxyguanosine (8-OHdG). Moreover, to explore the association between elevated levels of the aforementioned molecules with metabolic dysfunction and cardiovascular risk in a cohort of apparently healthy obese individuals.

2. Materials and methods

2.1. Ethical considerations

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of the College of Medicine, University of Duhok (reference number 30102024-9-12). Details concerning the study protocol, aim, and protocol were subject to prior thorough discussion by the members of the board. The logistic preparations began shortly after the approval had been obtained, followed by the sample collection period. All required modifications to the study protocol were submitted to the Research Ethics Committee for re-approval, thereby ensuring the avoidance of discrepancies and maintaining transparency in the conduct of the research.

2.2. Study subjects

A cohort of 90 participants of both genders, aged 18–60 years, were recruited for this case-control study. Body mass index (BMI) is a widely used predominant metric employed for obesity identification and classification within both clinical and public health contexts. This measure, which is calculated by dividing an individual's weight in kilograms by the square of their height in meters, provides a generalized indication of body fatness and is a valuable tool for epidemiological studies. In addition to BMI, there are alternative methodologies available for evaluating body composition and assessing obesity. Among these, bioelectrical impedance analysis (BIA) has gained traction, utilizing skin impedance measurements to estimate body fat percentage by analyzing the resistance of body tissues to electrical currents. Furthermore, the waist-to-hip ratio (WHR) is another complementary metric that evaluates fat distribution, specifically the ratio of the circumference of the waist to that of the hips. In

the present study, BMI was used as the primary metric for evaluating obesity among recruited participants and to ensure a standardized and objective approach to the identification of obesity within the study population [18].

Based on the BMI, subjects were divided into two categories: The study group represented healthy obese (BMI > 30 kg/m^2), and the non-obese (MBI < 25 kg/m^2) as healthy controls. A written consent form was obtained from all participants indicating their approval for participation. Then, each subject was required to fill in a closed-ended questionnaire, including information concerning demographic characteristics such as age, height, and weight. Participants with reported diabetes and hypertension were excluded from the study. Any control sample exhibiting abnormal glycemic and lipid profile parameters was excluded from the data analysis to maintain consistency.

2.3. Arterial blood pressure measurement

Arterial blood pressure (BP) was measured in each subject using a mercury manometer, following the standardized protocols set by the American Heart Association and the American College of Cardiology [19]. These guidelines were followed to ensure methodological consistency, precision, and reliability in the obtained measurements, thereby minimizing potential sources of variability and ensuring compliance with established best practices in cardiovascular assessment. The BP was checked twice in 5-minute intervals at rest. Based on the results, subjects were considered normotensive (systolic 110–119/diastolic 60–80 mmHg), elevated BP (120–129/60–80 mmHg), and hypertensive (>129/>90 mmHg).

2.4. Specimen collection

Following data collection, a 5-milliliter venous blood sample was collected from each participant after 8 hours of fasting and then put in a gel tube with no anticoagulants. Samples were then centrifuged at 1500 rpm for 5 minutes to obtain sera. The serum samples belonging to each participant were then divided into 2 aliquots. The first was analyzed for metabolic parameters, including fasting blood glucose levels and lipid profiles. The second aliquot was preserved in deep freezing conditions (−20 °C) for subsequent assays of other inflammatory and oxidative stress parameters.

2.5. Metabolic parameters

Fasting blood sugar (FBS) was measured as an indicator of glycemic status, with the reference range defined as 70–110 mg/dL according to the criteria recommended by the World Health Organization (WHO). A reading of 110 mg/dL or above was classified as hyperglycemia [20]. Furthermore, the lipid profile was evaluated by measuring total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL). The ratio of LDL to HDL (LDL/HDL) was calculated to determine cardiovascular risk, with ratios below 3 categorized as no risk, those between 3 and 5 as low risk, and ratios exceeding 5 as high risk. Quantitative analysis of fasting glucose and lipid profiles for each sample was performed using the automated analyzer (Cobas 6000, Roche Diagnostics). The levels of LDL and VLDL were determined using the Friedewald equation [21].

2.6. Inflammatory and oxidative stress biomarkers

High sensitivity C-reactive protein (hs-CRP) and soluble suppression of tumorigenicity-2 (sST2) were determined as candidate biomarkers for inflammation. The hs-CRP is an acute-phase protein synthesized by the liver in response to inflammation, while sST2 is the circulating form of the IL-33 receptor used to indicate poor prognosis in chronic inflammatory conditions. Both proteins were quantitatively measured using enzyme-linked immunosorbent assay (ELISA) (Shanghai Korain Biotech Co., Ltd). To explore the oxidative stress biomarkers, malondialdehyde (MDA) and 8-hydroxy-2-deoxyguanosine (8-OHdG) were quantitatively assayed in serum samples. MDA is commonly used as a marker of lipid peroxidation, while 8-OHdG is a predominant form of free-radical oxidative lesions elevated in response to oxidative nuclear and mitochondrial DNA damage. Serum MDA and 8-OHdG levels were measured using the colorimetric assay kit (Shanghai Korain Biotech Co., Ltd). A standard curve was constructed in accordance with the manufacturer's guidelines, and the optical density values were subsequently plotted to derive the final measurement.

2.7. Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 26.0 (Chicago, USA) was used for data analysis. Independent sample t-tests were used to determine the statistical differences between study groups, and the data were expressed as mean ± standard deviation. Descriptive statistics and frequencies were used to demonstrate the distribution of observations within variables and represent data in frequency (number) and percentage. Pearson's correlation coefficient was calculated to determine the association between variables, while the R-values were used to indicate the strength of the association. The statistical significance between study groups was determined by the probability value (p). In all statistical experiments, the values of ≤ 0.05 and ≤ 0.01 were considered significant and highly significant, respectively.

3. Results

Ninety individuals for both genders (18–60 years old) were recruited for this case-control study. Based on BMI, they were categorized as: A study group of 50 healthy obese (BMI > 30 kg/m^2) people and a control group of 40 non-obese (BMI < 25 kg/m^2) people. As illustrated in Table 1, age, weight, and BMI were significantly higher in the obese group than in controls ($p = 0.001$, 0.0001, and 0.0001, respectively). Concerning blood pressure, the mean systolic blood pressure (SBP) did not show any significant difference between groups, but the mean diastolic blood pressure (DBP) was substantially higher in the obese group ($p = 0.03$) compared to the control.

Table 1. Demographic features of the study groups.

Variables	Obese (N = 50)	Non-obese (N = 40)	p-value
Age	38.84 ± 9.681	28.19 ± 9.382	0.001
Height (CM)	162.88 ± 9.09	168.87 ± 10.77	0.03
Weight (Kg)	84.49 ± 14.47	63.28 ± 8.49	0.0001
BMI	31.83 ± 4.73	22.23 ± 1.72	0.0001
SBP	116.30 ± 12.4	112.50 ± 6.83	0.12
DBP	77.32 ± 10.09	72.50 ± 6.83	0.03

Among 50 obese subjects, 70% were male and 30% were female. The majority (60%) have lived in the countryside for the last 5 years, and the other 40% have lived in the city center. Regarding smoking habits, 72% were smokers regardless of gender and frequency, compared to 20% of non-smokers. Most of the obese subjects (66%) reported a history of family obesity and cardiovascular diseases (74%), and 32% had a family history of cancer (Table 2).

Table 2. Frequency of demographic characteristics among obese subjects.

Variables	Group (N = 50)	Frequency	Percent
Gender	Male	35	70
	Female	15	30
Living place	Center	20	40
	Countryside	30	60
Smoking	Yes	36	72
	No	14	28
Family history of obesity	Yes	33	66
	No	17	34
Family history of CVD	Yes	37	74
	No	13	26
Family history of cancer	Yes	16	32
	No	34	68

To explore the lipid and glycemic status, sera of recruited individuals were analyzed for FBS and lipid profile. FBS and triglyceride were significantly higher in the study group ($p = 0.01$ and 0.001) compared to the control. Concerning the cholesterol panel, LDL showed substantial elevation in obese subjects ($p = 0.001$), but HDL was remarkably reduced ($p = 0.02$) compared to non-obese. Moreover, total cholesterol and VLDL did not show significant differences between groups (Table 3). Concerning cardiovascular risk, the mean LDL/HDL was determined for both study groups. Although the study group exhibited a higher mean ratio than the control, this difference was not statistically significant.

Table 3. Glycemic and metabolic parameters among study groups.

Variables	Obese (N = 50)	Non-obese (N = 40)	p value
FBS	98.48 ± 15.37	88.75 ± 6.57	0.01
TC	179.42 ± 39.75	160.13 ± 38.59	0.09
TG	154.34 ± 75.97	84.88 ± 22.85	0.001
HDL	35.65 ± 8.59	41.51 ± 8.17	0.02
LDL	107.99 ± 33.09	84.62 ± 21.41	0.001
VLDL	29.59 ± 15.23	22.66 ± 14.88	0.12
LDL/HDL	3.16 ± 1.69	2.39 ± 1.25	0.07

To determine the incidence of obese subjects with abnormal lipid and glycemic controls, they were categorized based on the laboratory reference values. Normoglycemic subjects (FBS = 70–110 mg/dL) represented 90%, followed by 10% with hyperglycemia. Concerning the lipid panel, most (42%) had a satisfactory profile, 24% with hypertriglyceridemia, followed by hyperlipidemia (20%), and last,

hypercholesterolemia (14%). For cardiovascular risk, 60% had no risk, whereas the remaining 40% exhibited CV risk. Among the latter group, 24% had low risk, and the other 16% displayed high risk. In terms of blood pressure, most obese individuals (78%) were normotensive compared to 22% with elevated blood pressure (Table 4).

Table 4. Frequency of metabolic parameters in obese individuals.

Variables	Group (N = 50)	Frequency	Percent
Lipid status	Normal LP	21	42
	Hypercholesterolemia	7	14
	Hypertriglyceridemia	12	24
	Hyperlipidemia	10	20
Glycemic status	Normoglycemia	45	90
	Hyperglycemia	5	10
Blood pressure	Normotensive	39	78
	Elevated BP	11	22
Cardiovascular risk	Normal	30	60
	Low risk	12	24
	High risk	8	16

To investigate the existence of inflammation and oxidative stress in sera of healthy obese people, a panel of biomarkers was used (Table 5). Concerning inflammatory markers, both hs-CRP and sST2 were highly significantly elevated in obese individuals compared to controls ($p = 0.001$), except for WBC count, which did not display a statistical difference. MDA and 8-OHdG were used in this study as potential biomarkers for oxidative stress. Our findings indicated that both expressed statistically significant elevation in the study group compared to the control group ($p = 0.001$ and 0.000, respectively).

Table 5. Inflammatory and oxidative stress parameters among study groups.

Variables	Obese (N = 50)	Non-obese (N = 40)	p-value
WBC count	7.04 ± 1.81	6.85 ± 1.43	0.67
hs-CRP	5.01 ± 1.36	2.7 ± 0.33	0.001
sST2	6.65 ± 3.83	1.29 ± 0.71	0.001
8-OHdG	5.58 ± 2.14	2.53 ± 0.45	0.000
MDA	4.81 ± 0.98	2.88 ± 0.34	0.001

Pearson's correlation coefficient was used to assess the relationship between metabolic parameters and inflammatory/oxidative stress biomarkers. The strength of the correlation was represented by R-values, while the p-value indicated the statistical significance of the relationships between variables. As presented in Table 6, BMI had a positive correlation with all inflammatory and oxidative stress biomarkers, achieving statistical significance. FBS and triglycerides (TG) displayed a notable correlation with hs-CRP, 8-OHdG, and MDA but not with sST2. Furthermore, HDL, LDL, VLDL, and LDL/HDL showed a statistically significant positive correlation with hs-CRP and MDA. Last, TC was positively correlated with hs-CRP.

Table 6. Correlation coefficient between study variables.

Variables	hs-CRP	sST2	8-OHdG	MDA
BMI	0.473	0.368	0.385	0.472
	(0.0001)	(0.002)	(0.001)	(0.0001)
FBS	0.335	0.193	0.335	0.411
	(0.01)	(0.12)	(0.01)	(0.001)
TC	0.366	0.03	0.143	0.486
	(0.005)	(0.77)	(0.25)	(0.0001)
TG	0.697	0.220	0.260	0.563
	(0.0001)	(0.07)	(0.03)	(0.0001)
HDL	−0.597	−0.162	−0.128	−0.302
	(0.0001)	(0.19)	(0.3)	(0.01)
LDL	0.470	0.07	0.112	0.517
	(0.001)	(0.56)	(0.4)	(0.0001)
VLDL	0.292	0.08	0.159	0.267
	(0.02)	(0.59)	(0.21)	(0.04)
LDL/HDL	0.701	0.007	0.09	0.466
	(0.0001)	(0.95)	(0.47)	(0.001)

Table 7 demonstrates the correlation between inflammatory and oxidative stress parameters. Our results revealed a positive correlation between 8-OHdG and the inflammatory markers hs-CRP and sST2, with p-values of 0.0001 and 0.004, respectively. Moreover, MDA also exhibited a positive association with these inflammatory biomarkers, with p-values of 0.01 and 0.02, respectively.

Table 7. Correlation coefficient between inflammatory and oxidative stress markers.

Variables	hs-CRP	sST2
8-OHdG	0.473	0.349
	(0.0001)	(0.004)
MDA	0.335	0.281
	(0.01)	(0.02)

4. Discussion

Obesity has emerged as a global epidemic and a major risk factor for various chronic conditions, including insulin resistance, type 2 diabetes, and cardiovascular diseases. Furthermore, it is linked to a diminished quality of life and escalating healthcare costs [22]. The global increase in obesity prevalence remains a perplexing phenomenon, primarily attributed to an imbalance between energy intake and expenditure. Notably, approximately 5% of individuals achieve sustained weight reduction following dietary interventions [23]. Consequently, obesity can be understood as a complex network of systemic pathologies involving multiple organs, leading to metabolic decline. Given the limited data on individuals who are obese yet healthy, we aimed to investigate a panel of mediators (sST2 and 8-OHdG) as potential novel biomarkers for low-grade inflammation and oxidative stress while examining their associations with glycemic and metabolic parameters in a sample of apparently healthy obese and normal-weight individuals.

Recruited subjects were classified into healthy obese (BMI > 30 kg/m^2) as a study group and non-obese (BMI < 25 kg/m^2) as controls. Our results indicated that the FBS was considerably higher in the study group despite being within the reference range. Mechanistically, excess plasma concentrations may lead to increased energy intake and reduced energy expenditure due to the failure to stimulate leptin production. Elevated blood glucose levels are associated with dyslipidemia, fatty liver, decreased insulin sensitivity, and hyperuricemia [24]. Concerning the prevalence of dyslipidemia among obese subjects, 58% exhibited abnormal lipid profiles, including hypercholesterolemia, hypertriglyceridemia, and hyperlipidemia, compared to 42% with normal lipids. Furthermore, the mean TG and LDL were significantly higher, while the HDL was remarkably lower in obese subjects than controls. This aberration in lipid profile can predispose to many cardiovascular complications, mainly coronary heart disease (CHD) [25]. Moreover, subjects exhibiting persistent dyslipidemia, a well-established predictor of CHD, face a considerably higher risk for the development of that disease [26]. Obesity is consistent with unfavorable plasma lipids, which could be a risk factor for diabetes and hypertension [27]. Insulin resistance seems to be the main player orchestrating metabolic dysregulation in obesity. It reduces the ability of insulin to suppress hormone-sensitive lipase in adipose tissues and subsequently leads to increased breakdown of TG and free fatty acid (FFA) release. Elevated FFAs are released into the blood circulation and transported back to the liver. There, it results in increased synthesis of atherogenic LDL and VLDL, and decreased clearance of TG-rich lipoproteins [28].

Despite the well-documented role of inflammation in obesity, we aimed to investigate sST2 as a potential novel marker for low-grade inflammation and its correlation with other immunometabolic alterations in apparently healthy obese individuals. Concerning other inflammatory markers, we also investigated high-sensitivity C-reactive protein (hs-CRP). The sera of obese individuals exhibited significantly higher levels compared to normal-weight individuals. Moreover, it showed a positive correlation with BMI, FBS, and other metabolic parameters. These findings are consistent with other studies emphasizing that plasma CRP levels are remarkably elevated in obesity. In addition to being a major source of IL-1, docking studies confirmed CRP interaction with the extracellular domain of the leptin receptor, which explains the lack of response to leptin during obesity [29]. Elevated CRP levels are associated with obesity and reduced quality of life among the Korean population [30]. In a meta-analysis of randomized controlled trials, CRP was remarkably reduced 12 weeks after calorie-restricted diet intake [31].

Soluble suppression of tumorigenicity-2 is a ligand for IL-33, the pro-inflammatory cytokine that belongs to the IL-1 family. While there are very few clinical studies that entail the validity of sST2 as a potential marker of inflammation in obesity, it has been well-established as a marker of poor prognosis in patients with heart failure, coronary artery disease, and diabetes mellitus [32]. The sST2/IL-33 axis has been extensively studied and shown to play crucial roles in various inflammatory, cancer, and cardiovascular diseases. sST2 is involved in the maintenance of homeostasis and the progression of multiple disorders by counterbalancing the activation of the IL-33/ST2L axis, which is triggered during the development of fibrosis, tissue damage, and inflammation, as well as remodeling [33].

In this study, we aimed to assess serum levels of the aforementioned inflammatory pleural (mediators) in a cohort of obese and non-obese subjects. Serum sST2 levels were substantially elevated in obese subjects, which correlated positively with BMI. Even though limited data are available linking sST2 and obesity, it has been suggested that sST2 and IL-33 are expressed in adipose tissues (AT) in response to inflammation [34]. In murine models of obesity, IL-33 has shown protective effects characterized by reducing adiposity and improving insulin tolerance. It is commonly thought that sST2 interacts with

its ligand (IL-33) during obesity, thus blocking its biological effects [35]. Demyanets et al. are the only researchers who have investigated sST2 as a marker for inflammation in obesity. The circulating sST2 levels, among other inflammatory mediators, are associated with markers of lipid metabolism and liver functions in obese individuals. Moreover, sST2 levels significantly reduced one year after successful bariatric surgery [36]. The above-mentioned data collectively highlight the notable association between sST2 elevation in response to low-grade inflammatory immune response and obesity.

After validating the existence of low-grade inflammation in obesity, it is essential to highlight the possible mechanism behind the substantial elevation in inflammatory mediators. White adipose tissues (WAT) are endocrine organs that secrete various types of adipokines and cytokines, which in turn regulate various physiological pathways such as insulin signaling, glucose uptake, and fatty acid oxidation [37]. In obesity, the WAT undergoes a phenotype switch characterized by infiltration of immune cells and dysfunctional adipocytes. The inflamed ATs secrete pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α locally and systematically, disrupting AT homeostasis [38].

Researchers have thoroughly explored the relationship between obesity and oxidative stress. Molecules such as reactive oxygen species (ROS) play a key role in various oxidative stress signaling pathways, including nuclear factor kappa B (NF-κB), Janus kinase/signal transducers and activators of transcription (JAK-STAT), and nuclear factor erythroid 2-related factor 2 (Nrf-2), leading to an increase in adipocyte size, promoting adipogenesis and adipocyte differentiation [39]. Moreover, the signaling pathways phosphoinositide 3-kinase (PI3-kinase) and protein kinase B (Akt) are activated upon prolonged exposure of adipocytes to ROS, impairing pancreatic islet function [40]. Adipose tissue accumulation and metabolic dysfunction are therefore considered early triggers for the induction of oxidative damage [41].

We investigated MDA and 8-OHdG as potential biomarkers for oxidative stress. Our findings indicated that the sera levels of both mediators were significantly elevated in obese individuals compared to the normal-weight control individuals. In addition to BMI, MDA was positively correlated with all metabolic parameters except total cholesterol, while 8-OHdG was associated only with BMI, FBS, and TG. Moreover, both biomarkers showed a significant positive correlation with hs-CRP and sST2. Despite being a well-known candidate as the end product of lipid peroxidation, limited studies link MDA to obesity. In a national cohort of the Chinese population, elevated blood MDA levels are associated with diastolic blood pressure and BMI [42]. A regression analysis by Prázný et al. reported that BMI is a significant predictor of elevated plasma MDA in type-2 diabetes [43].

In nuclear and mitochondrial DNA, 8-OHdG is a predominant form of free-radical oxidative DNA damage, which has been widely used as a reliable biomarker for oxidative stress and carcinogenesis [44]. This prominence is primarily attributable to guanosine, the nucleobase associated with 8-OHdG, which encounters higher degrees of oxidation than other DNA bases. Consequently, 8-OHdG levels serve as a crucial indicator of oxidative stress and its potential impact on genomic integrity. Elevated levels of urinary 8-OHdG have been associated with various pathological conditions, including cancer, atherosclerosis, hypertension, and diabetes. Therefore, it suggests an increased oxidative stress state within the body, which can lead to cellular damage and contribute to disease progression [45]. Nevertheless, limited evidence is pleural regarding its relationship with metabolic dysfunction in obesity. A randomized, placebo-controlled clinical trial is considered one of the occasional studies in the literature highlighting the direct relationship between 8-OHdG and obesity. It was reported that plasma 8-OHdG levels dramatically reduced after metformin treatment in women with polycystic ovary syndrome (PCOS) compared with the placebo [46]. Moreover, increased plasma 8-OHdG

concentrations are consistent with increased levels of inflammatory cytokines, mainly IL-6 and TNF-α, in obese subjects. This elevation is also associated with a hypertensive state [47].

This study stands out as the first of its kind to explore a panel of novel inflammatory mediators in the context of obesity within the region; however, it does have limitations. A larger sample size would enhance the conclusiveness and robustness of the findings, as clinical studies benefit from broader participant groups. The primary challenges included logistical preparations and difficulties in prompting individuals to participate in the research. Despite the initial recruitment of more than 90 participants, many were excluded based on the criteria outlined in the materials and methods, such as having cardiovascular disorders or diabetes. Additionally, while we aimed to employ advanced techniques to investigate the molecular aspects of inflammation, such as PCR, we were hindered by financial constraints and a lack of support from official educational authorities. Despite these limitations, this study provides the first clinical evidence in the region and is one of the few studies on a global scale examining sST2 and 8-OHhG as potential biomarkers of inflammation and oxidative stress in a cohort of healthy obese individuals.

5. Conclusions

A novel investigation was conducted for the validity of mediators hs-CRP, sST2, MDA, and 8-OHdG as potential biomarkers of inflammation and oxidative stress in healthy obese individuals. This study provides the first clinical evidence in the region, providing valuable insights into the interplay between obesity and the systemic inflammatory immune response. The elevated levels of these biomarkers are closely associated with metabolic dysfunction, reflecting adipose tissue inflammation. Furthermore, the disruptions in metabolic processes not only highlight the underlying mechanisms linking obesity to systemic inflammation but also underscore the potential for increased cardiovascular risk over time. Our findings emphasize the importance of early identification and targeted intervention in obese populations to alleviate long-term cardiovascular complications.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

The Majeed K collected data and specimens and conducted the laboratory measurements. Majeed K and Ali H analyzed the data and wrote the first draft. Ali H designed the study, edited the manuscript, and supervised the project.

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