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Characterization of the oxidative stress and inflammatory markers in metabolically healthy obese individuals

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Abstract: *Obesity has emerged as a global health problem. Although various studies have linked obesity to a wide spectrum of diseases mainly diabetes and cardiovascular disease, little is known concerning involvement of oxidative stress and inflammation in non-diseased conditions. The current study aims to evaluate the levels of inflammatory and oxidative stress markers in sera of healthy obese individuals.*
A case control study involved fifty healthy obese and fifty normal weight individuals. After obtaining relevant clinical data, sera were taken for further laboratory investigations including lipid profile, fasting serum glucose and HbA1c. Samples were also investigated for determining inflammatory and oxidative stress markers including highly sensitive C - reactive protein (hs-CRP), malondialdehyde (MDA) and gamma glutamyl transferase (GGT).
Total cholesterol, triglyceride and fasting blood glucose levels were significantly higher in healthy obese individuals compared to normal weight controls ($p < 0.0001$, 0.009 and < 0.0001 respectively). The hs-CRP, MDA and GGT were also statistically significantly higher in healthy obese ($p < 0.001$, 0.005 and 0.001 respectively). Moreover, MDA was positively correlated with GGT and was statistically significant ($p < 0.001$). The obtained findings suggest that, there may be an existence of a low grade chronic inflammation consistent with oxidative stress which might be considered as a risk factor for developing metabolic diseases and cardiovascular disturbances mainly diabetes mellitus, hypertension and stroke.

Keywords: *obesity, inflammation, oxidative stress, body mass index*

1.Introduction

Obesity has become one of the serious public health problems worldwide. It is defined as a massive accumulation of triacylglycerols in adipose tissues as a result of excessive energy intake compared to energy usage (1). Recent statistics indicate that the total number of population has exceeded 2 billion obese constituting around 30% of the whole population globally. The Global Burden of Diseases in 2017 reported that the number of obese people have doubled in more than 70 countries since 1980 (2). This condition has a predominantly genetic basis and could probably be attributed to polygenic aspects. Other predisposing factors include higher energy intake and decreased physical activity

(3). While the physical consequences of obesity, such as arthritis, are debilitating and costly, the metabolic consequences mainly include insulin resistance, diabetes, fatty liver disease, coronary artery disease, hypertension and polycystic ovary syndrome (4).

Although numerous research have linked obesity to a wide spectrum of diseases (5), little is known concerning the role of inflammation and oxidative stress in obesity particularly in people who are metabolically healthy. Concerning inflammation, the traditional theory indicates that the basal systemic inflammation is gradually developed as people become older referring to the term infalmmaging (6). The precise mechanism may be due to the contribution of inflammaging towards increasing risk of developing chronic diseases. However, this condition can be improved through non-pharmacological intervention strategies such as healthy diet consumption and physical activity performance (7). However, the current study will focus more on investigating the inflammation in young healthy obese individuals.

Oxidative stress is an imbalance between oxidative and anti-oxidative status in cells and tissues resulting in over production of free radicals and reactive oxygen species (ROS) (8). Excessive production of ROS molecules may attack cellular proteins and nucleic acids leading to cellular dysfunctions and subsequently loss of energy metabolism (9). It was reported that even high fat diet such as carbohydrates may promote generation of oxidative stress molecules represented by elevation in lipid peroxidation products coupled with a decrease in cellular anti-oxidant capacity which eventually increase the risk for developing chronic diseases (10).

Exploring oxidative stress and the inflammatory status in healthy obese will provide researchers with further insights towards better understanding of factors that predispose or protect obese individuals from metabolic disturbances. Moreover, will create ideas for therapeutic interventions that could eventually improve the life quality of obese people. Taking this idea into consideration, the aim of the present study is to evaluate the role of inflammation and oxidative stress status in metabolically healthy obese as wells as assessment of glycemic and lipid status. Additionally, to find out the feasibility of any possible correlation between these markers and the metabolic status.

METHODS:

Subjects:

Following obtaining appropriate approval concerning research conduction ethics, the study was conducted. This case control study involved one hundred apparently healthy individuals; fifty obese with body mass index (BMI) > 30 kg/m² and fifty non-obese with BMI <25 kg/m². Excluding criteria were hypertension, diabetes, smokers, pregnancy as well as people with history of cardiovascular disorders. A pre-requested questionnaire was filled in for each participant including basic demographic characteristics such as height, weight in addition to other necessary information. Arterial blood pressure was measured for study participants at resting condition using traditional mercury sphygmomanometer.

Specimen collection and storage:

Five milliliters of venous blood was collected after ten hours of fasting in plain test tubes without anticoagulant. After coagulation, samples were centrifuged (at 1500 rpm for 5 min). The separated serum for each sample was divided into two aliquots. One is designated for the immediate assay of fasting glucose and lipid profile biomarkers. The other aliquot was stored at -20 C for subsequent assays such as highly sensitive C - reactive protein and other biomarkers.

Laboratory tests:

Glycemic and lipid profile biomarkers including fasting serum glucose level, total

cholesterol (Tch), triglyceride (TG) and high density lipoprotein cholesterol (HDL) were assayed by automatic analyzer (Cobas 6000). Low density lipoprotein cholesterol (LDL) was calculated according to "Friedewald" equation (11).

Assessment of inflammatory markers included highly sensitive C-reactive protein (hs-CRP), assayed by enzyme linked immunosorbent assay "ELISA" using commercial kit (Monobind Inc., USA). The candidate markers for oxidative stress included malondialdehyde (MDA), a marker for lipid peroxidation as well as serum gamma glutamyl transferase (GGT). MDA was measured manually using thiobarbuturic acid method whereas GGT was measured using spectrophotometric method (Biolab, France).

Statistical analysis:

Statistical analysis was performed using statistical package for social sciences (SPSS) Version 18 (Chicago, USA). All variables were expressed as mean ± standard deviation. The clinical significance between study groups was determined using *p* value. The *p* values of 0.05 or less were considered statistically significant whereas the *p* values of 0.001 or less where considered statistically highly significant.

RESULTS:

The current study involved a total of one hundred participants divided in to two groups; the study group included fifty obese individuals whereas the control group represented 50 non obese. The study group had the mean age of 33 years vs. 31 years for controls. Both weight and body mass index (BMI) were statistically significantly higher in study group ($p < 0.0001$) compared to controls. Both systolic and diastolic blood pressure didn't show any significant difference between study groups ($p = 0.097$ and 0.163) respectively (table 1).

Table 1: Demographic characteristics of study groups

Variables	obese (no 50)	non-obese (no 50)	*P* value
Age (years)	33 ± 7.13	31 ± 6.25	0.139
Height (cm)	160 ± 5.04	162 ± 6.53	0.089
Weight (kg)	79.51 ± 12.14	64.2 ± 10.23	< 0.0001
Body mass index (kg/m²)	31.1 ± 4.27	24.5 ± 3.63	< 0.0001
Systolic blood pressure (mmHg)	118 ± 3.28	117 ± 3.88	0.097
Diastolic blood pressure (mmHg)	76.7 ± 3.81	75.3 ± 4.22	0.163

Concerning lipid profile variables, both total cholesterol and triglyceride were statistically significantly higher in healthy obese compared to non-obese controls ($p < 0.0001$ and 0.009) respectively. Other biomarkers including high density lipoprotein, low density lipoprotein and very high density lipoprotein showed no significant difference between study groups. The glycemic biomarker represented by serum blood glucose displayed a statistically significant elevation in study group compared to controls ($p < 0.0001$), however, the hemoglobin A1c (HbA1c) was not statistically significantly different between study groups (table 2).

Table 2: Lipid profile and glycemic biomarkers of study groups

Variables	obese (no 50)	non-obese (no 50)	*p* value
Total cholesterol (mg/dl)	183.51 ± 11.19	151.22 ± 14.8	< 0.0001
Triglyceride (mg/dl)	100.62 ± 13.5	92.3 ± 11.9	0.009
High density lipoprotein (mg/dl)	48.58 ± 7.06	47.12 ± 7.4	0.476
Low density lipoprotein (mg/dl)	84.95 ± 4.51	84.65 ± 5.45	0.998
Very low density lipoprotein (mg/dl)	18.44 ± 1.9	18.48 ± 2.1	1.001
Fasting blood glucose (mg/dl)	95.22 ± 8.14	78.39 ± 9.43	< 0.0001
HbA1c	5.32 ± 0.43	5.25 ± 0.51	0.459

Both candidate biomarkers for oxidative stress; malondialdehyde and gamma GT were statistically significantly higher in healthy obese compared to non-obese controls (p = 0.005 and 0.001 respectively). Moreover, highly sensitive C - reactive protein was also statistically significantly higher in study group ($p < 0.001$) compared to controls (table 3).

Table 3: Oxidative stress and inflammatory markers among study groups.

Variables	obese (no 50)	non-obese (no 50)	*P* value
Malondialdehyde (ng/ml)	5.37 ± 0.98	2.11 ± 0.81	0.005
Gamma GT (mg/dl)	32.77 ± 5.73	27.89 ± 6.11	0.001
Highly sensitive c-reactive protein (mg/dl)	6.44 ± 1.53	2.98 ± 1.09	< 0.001

Pearson's correlation coefficient was used to find out the possible correlation between oxidative stress markers with the inflammatory hs-CRP. Interestingly, there was a statistically significantly positive correlation between MDA and GGT (r = 0.461 and $p < 0.001$) whereas the correlations between MDA – CRP and CRP – GGT were not significant (Table 4).

Table 4: Pearson's correlation coefficient between inflammatory and oxidative stress biomarkers

Variables	***r*** value	*p* value
MDA – GGT	0.461	< 0.001
MDA – CRP	0.189	> 0.05
CRP – GGT	0.152	> 0.05

Lastly, table 5 shows the correlation between BMI and inflammatory hs-CRP and oxidative stress markers. All markers showed a weak positive correlation with BMI except for GGT which displayed a moderate positive correlation and was statistically significant (r = 0.27 and $p < 0.05$).

Table 5: Pearson's correlation coefficient between BMI with inflammatory and oxidative stress

Variables	***r*** value	*p* value
BMI - MDA	0.04	0.782
BMI - GGT	0.27	< 0.05
BMI - CRP	0.05	0.730

DISCUSSION:

Obesity has emerged as a global epidemic in the last decades. The reason behind that could be due to its obvious association with a variety of diseases mainly diabetes mellitus, cardiovascular diseases, nonalcoholic fatty liver disease (NAFLD), immune disorders and even cancer. This results in reduction in quality of life as well as shortened life span of people developing obesity 12, 13). Since it is apparent that extensive preclinical and clinical studies have confirmed the association between obesity with different categories of diseases, the aim of the present study was to determine the status of inflammation and oxidative stress in healthy obese individuals.

The demographic data confirmed the inclusion criteria of the study participants being apparently metabolically healthy individuals. The control group involved healthy people with normal body mass index to clearly identify the differences in biochemical and other laboratory parameters among study groups. Concerning the lipid profile status, obese populations had higher levels of serum total cholesterols and triglyceride compared to non-obese controls.

Since both groups are healthy subjects, this kind of elevations in lipid profile parameters could be attributed to dietary habits including excessive consumption of saturated fats and carbohydrates, smoking, alcohol intake and inadequate physical exercise (14, 15). Genetics may play a significant role in the development of elevated serum cholesterol levels such as familial hypercholesterolemia (FH) which is an autosomal dominant characterized by a substantial elevation in cholesterol and LDL levels from birth. It occurs as a result of genetic mutations in the LDL receptors or apolipoprotien B genes leading to a decrease in LDL metabolism (16, 17). Concerning the

glycemic status, the obese population displayed a higher levels in fasting blood glucose (except HbA1c) compared to normoglycemic controls. People with impaired fasting glucose are at a high risk for developing diabetes mellitus as well as cardiovascular diseases (18). Rhee et al. reported an association between obesity and glycemic status with developing heart failure in Korean population. It was concluded that people with elevated glucose levels and those with diabetes displayed an increased risk for developing heart failure compared to normoglycemic individuals (19).

C-reactive protein (CRP) is an acute phase protein that is considered a non-specific marker for inflammation. Its serum levels are elevated in all diseases involving activation of the inflammatory immune response mainly acute bacterial infections and autoimmune diseases (20). Our results indicated that the serum hs-CRP levels were substantially elevated in obese subjects compared to non-obese controls. The findings are consistent with previous studies showed that obesity is associated with elevated CRP levels. This association seems to be stronger in women specifically North American and Europeans (21). Another study revealed that the CRP levels were more elevated in depressive obese compared to non-depressives among German population (22). There are numerous studies that link CRP levels to obesity, decreased quality of life as well as cardiovascular disorders (23, 24). However, the only study found in the literature that investigated the CRP levels in healthy population was previously reported by McGill and Gronowski (D25). It was concluded that even healthy obese develop increased levels of hs-CRP which was positively correlated with BMI.

Oxidative stress can result from imbalance between both pro-oxidant and antioxidant factors. To evaluate the oxidative stress status, two markers were used; malondialdehyde (MDA) and Gamma glutamyl transferase (GGT). The first one is widely used to assess the lipid peroxidation (a form of oxidative stress) in biological samples whereas the later represents one of the essential lever enzymes. The current results emphasized that both markers were statistically significantly higher in the sera samples of obese individuals compared to control. These findings are in concordance with previous studies concluding that pronounced oxidative stress parameters such as myeloperoxidase activity (MPO) and nitric axide levels were documented in obese people compared to controls (26). It was also reported that elevated MDA levels were positively associated with elevated diastolic hypertensive patients (27). Moreover, increased oxidative stress in accumulated fat was shown to be considered as an early initiator for metabolic syndrome (28). The current study revealed a positive correlation between MDA and GGT levels. This seems rational and supported by previous studies highlighting the validity of both parameters as early markers for oxidative stress and their association to cardiovascular diseases (29, 30).

After determining the role of inflammation and oxidative stress, the important question remains to be answered; what is the precise mechanism underlying these events. Moreover, what is the possible explanation behind the coexistence of these two essential players? The classical theory reveals that the accumulated adipose tissues respond to the highly diet intake by initiating an innate immune response. However, looking at the whole picture, the precise molecular mechanism may be explained by two possible points. Firstly, changes in the phenotype of the white adipose tissue (WAT) upon weight gain. This results in phenotype switch of WAT characterized by appearance of dysfunctional adipocytes initiating pro-inflammatory cytokine release and subsequently activating a low grade inflammatory immune response (31). Secondly, infiltration of the innate immune cells particularly macrophages into the already dysfunctional and inflamed adipocytes further exacerbates the condition. As a result, the inflamed adipose tissues become a reliable

source for secreting pro-inflammatory cytokines mainly interleukin 1 (IL-1), tumor necrosis alpha (TNF-α) and interleukin 6 (IL-6) (32, 33). This low grade chronic inflammation results in altered metabolism that is also known as "metainflammation" (34).
Concerning the involvement of oxidative stress, the generated molecules results in cellular dysfunctions represented by altered cell signaling pathways, genetic mutations, impaired DNA damage eventually leading to reduction in biological activity, immune activation and inflammation (35, 36). Overall, long term existence of low grade chronic inflammation and oxidative stress in healthy obese can lead to initiation of pathologic milieu and subsequently increasing risk for developing chronic diseases.

CONCLUSION:

The current study is considered one of the very few of its kinds documenting the presence of inflammation and oxidative stress in apparently healthy obese. The findings conclude that there may be an existence of a low grade chronic inflammation consistent with oxidative stress which might be considered as a risk factor for developing metabolic diseases and cardiovascular disturbances mainly diabetes mellitus, hypertension and stroke. Future studies should focus on investigating the molecular insights and detailed signaling pathways underlying these metabolic changes. Thorough understanding of the pathophysiology of these events may provide further insights towards developing therapeutic interventions.

Conflicts of interest:

No conflicts of interest were reported.

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