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'ISCHAEMIA-MODIFIED ALBUMIN': A BIOMARKER OF OXIDATIVE STRESS IN OBESE INDIVIDUALS

Biochemistry

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ABSTRACT

BACKGROUND: Obesity is characterized by deposition of excess fat in the body . It is a chronic state of free radical formation through diverse pathways. Oxidative stress may be the unifying mechanism underlying the development of co-morbidities in obesity. The sources of oxidative stress observed in obesity are hyperglycemia, increased tissue lipid levels, increased free radical formation and chronic inflammation. The increased free radicals cause increased oxidative stress. This alters the serum albumin forming 'Ischaemia-modified albumin' (IMA).
OBJECTIVE: The objective of this study was to correlate IMA with Body mass index (BMI) and IMA with Malondialdehyde (MDA)
MATERIAL AND METHOD: The study was conducted in tertiary care hospital. A total of 105 subjects were divided into 3 groups based on BMI , according to standard clinical definition into : normal weight(controls), overweight and obese. Blood samples were taken to measure serum IMA, plasma malondialdehyde, serum lipid profile and plasma fasting glucose.
RESULT: The present study showed that the levels of IMA, malondialdehyde, fasting glucose were significantly raised in overweight and in obese group as compared to normal weight controls. Highly significant correlations were seen between IMA and BMI and between IMA and MDA.
CONCLUSION : As there is a positive correlation observed between IMA and MDA ,which is a known oxidative stress marker, IMA can be used as an oxidative stress marker in obesity.

KEYWORDS

obesity, oxidative stress, IMA

INTRODUCTION

The global epidemic of overweight and obesity 'globesity' is rapidly becoming a major public health problem in many parts of the world. Paradoxically, coexisting with undernutrition in developing countries, the prevalence of overweight and obesity a risk factor for chronic diseases like diabetes mellitus, stroke, hypertension and certain cancers, arthritis,etc. [1]

Obesity and overweight are defined as abnormal or excessive fat accumulation. The excess of adipose tissue (determined by the BMI), releases several products such as unesterified fatty acids, cytokines, plasminogen activator inhibitor-[1], adiponectin and IL-6 which exacerbate some associated conditions such as insulin resistance, dyslipidemia, endothelial dysfunction and cardiovascular disease. Such conditions are possible mechanisms that generate oxidative stress in obesity.[2,3]

Oxidative stress is an imbalance between tissue oxidants (free radicals or reactive oxygen species) and antioxidants, produced as result of bad eating habits, sedentary lifestyle, stressful life and certain genetic factors. The human serum albumin plays an important role in the efficient antioxidant defence of the body.[4]

Oxidative stress characterized by over production of free radicals like reactive oxygen species and specifically OH..(hydroxyl ion) may chemically modify the N-terminal region of human serum albumin, generating 'Ischaemia-modified albumin' (IMA).[5]

Ischaemia-modified albumin, a sensitive marker of ischemia has been studied in various diseases. It has been shown to be a sensitive biochemical marker of rapidly growing interest , especially for the diagnosis of myocardial ischaemia[6]. However emerging investigations suggest that apart from being a marker of cardiac ischemia ,IMA levels are also higher in diabetic[7] and hypercholesterolemic patients[8] and also in patients with metabolic syndrome[9] as shown by certain studies .

Malondialdehyde (MDA) , the end product of lipid peroxidation is a known oxidative stress marker which has been shown to be raised in obesity and other situations with oxidative stress[10,11]. Lipid profile is also usually deranged in obese subjects .

But IMA has not been extensively studied in obese subjects in India. Keeping this paucity in mind this study was designed to determine the correlation between IMA and BMI and also IMA and MDA .

Materials and Methods

The study included 105 subjects falling in the age of 21-55 years group taken from OPD and indoor patients coming to our tertiary care hospital. They were divided into three equal groups according to their Body Mass Index (calculated as weight in kilograms divided by height in metres). The groups were based on standard clinical definition: normal weight individuals (18.5-24.9 kg/m^2); overweight individuals (25.0 – 29.9 kg/m^2) ; obese individuals ($\geq$ 30 kg/m^2). The normal weight individuals were taken as age and sex matched healthy controls. The subjects on any antioxidant therapy and statin therapy, patients of diabetes, hypertension ,acute coronary syndromes, stroke were excluded from the study.

All details of study were explained to subjects and informed written consent was obtained and all studies were done in accordance with the guidelines approved by the local research ethics committee. About 5 ml of blood samples were collected after 12 hours of fasting. Venous blood sample was withdrawn from the ante-cubital vein of each participant after taking all aseptic precautions using sterile needles and syringes. Haemolysed samples were excluded. The blood samples were immediately transferred to a clean dry sterile plain bulb, fluoride bulb and EDTA tubes. Blood specimens in plain tubes were allowed to clot for 30 minutes and then were centrifuged and aliquots of serum samples were stored at -200c till the time of measurement of IMA , triglycerides, total cholesterol, HDL cholesterol (HDL-C). Serum IMA was measured by a colorimetric cobalt –albumin binding assay on a spectrophotometer at 470 nm . Triglycerides, total cholesterol and HDL cholesterol were estimated on XL-640 auto analyzer (Transasia biomedicals Ltd ., India). LDL cholesterol (LDL-C) and VLDL cholesterol (VLDL-C) were then calculated using Friedewald's equation. Blood samples collected with EDTA were used to analyze plasma malondialdehyde (MDA) immediately after collection by thiobarbituric acid method . Blood samples from fluoride bulb were used to measure fasting glucose immediately which was analyzed on XL-640 auto analyzer.

Results

Continuous variables age, anthropometric and biochemical parameters were presented as mean ± standard deviation (mean ± SD). Categorical variable (gender) was expressed in actual numbers. Demographic, anthropometric and biochemical parameters were compared between 3 categories of BMI by performing oneway ANOVA for normalized data. Bonferroni t-test (Multiple comparison test) was performed to compare the mean values between any 2 categories of BMI. Categorical variables were compared by Chi-

square test. Pearson's correlation coefficient (r) was calculated to assess the nature and strength of correlation between IMA and anthropometric and other biochemical parameters. Statistical software STATA version 13.0 and Microsoft Office Excel 2007 software were used for data analysis.

In the present study, the IMA levels were highly significantly elevated in overweight and obese group as compared to the normal controls. ($p<0.001$) There was significant positive correlation between IMA and BMI ($r=0.8501$, $p<0.0001$) The MDA levels were also highly significantly raised in overweight and obese as compared to the controls. ($p<0.001$) .A significant positive correlation was found between IMA and MDA. ($r=0.7625$, $p<0.0001$). There was highly significant rise in fasting glucose in overweight and obese as compared to controls ($p<0.001$). A significant positive correlation was observed between fasting glucose and IMA .($r=0.2756$, $p<0.01$). Serum triglyceride was significantly elevated in the overweight and obese group as compared to the control. ($p<0.05$). There was no significant rise in total cholesterol and LDL-C as compared to the control group. ($p>0.05$) The HDL-C was significantly lower in the overweight and obese as compared to the controls. ($p<0.01$)There was no significant positive correlation seen between IMA and TC($r=0.0612$, $p>0.05$), IMA and triglycerides ($r=0.1336$, $p>0.05$), IMA and LDL-C ($r=0.1316$, $p>0.05$), while a significant negative correlation was present between IMA and HDL-C. ($r= -0.3569$, $p<0.001$).

Table 1: Mean values of different parameters

	Normal (Controls)	Overweight	Obese
IMA (ABSU)	0.37 ±0.10	0.47± 0.05	0.61± 0.07
MDA (nmol/ml)	3.89 ±0.69	6.83± 0.84	8.89± 1.15
Fasting glucose(mg/dl)	99.88 ±15.14	127.94 ±48.04	134.71± 55.53
Triglycerides (mg/dl)	81.97 ±33.15	119.22± 75.26	108.17± 56.59
Total cholesterol (mg/dl)	157.25± 26.21	168.85± 29.13	162.71± 24.98
HDL-C (mg/dl)	44.71± 8.87	37.2± 7.99	37.02 ±8.72
LDL-C (mg/dl)	95.8± 24.33	108.74± 22.36	104.2± 23.67

Table 2: Correlations between IMA and other parameters

No.	Parameters	Pearson r	p-value	Significance
1	**BMI**	0.8501	< 0.0001	yes
2	**WC**	0.7042	< 0.0001	yes
3	**MDA**	0.7625	< 0.0001	yes
4	**Fasting glucose**	0.2756	0.0044	yes
5	**Triglycerides**	0.1336	0.1742	no
6	**Total cholesterol**	0.0612	0.5352	no
7	**HDL-C**	-0.3569	0.0002	yes
8	**LDL-C**	0.1316	0.1808	no

Discussion

Obesity is a chronic inflammatory condition of adipose tissue accompanied by oxidative stress.[3] Oxidative stress is a condition in which the cellular production of reactive oxygen species (ROS: sometimes referred to as 'free radicals') exceeds the physiological capacity of the antioxidant defence system to render ROS inactivate.[10] Several studies have shown association between obesity and oxidative stress. They postulated the different mechanisms of development of oxidative stress in obesity. The possible contributors of oxidative stress in obesity are also associated with the onset of obesity related diseases.[12]

Various oxidative stress biomarkers have been studied in obesity and correlated with BMI.[11,12] In view of the present day evidence, Ischemia Modified Albumin (IMA) is accepted as a marker of oxidative stress and it has been determined to be associated with other oxidative stress markers.[5] IMA is not tissue specific and is elevated in subjects who undergo oxidative stress even without any evidence of cardiac ischemia.[7,13] IMA, a proven marker for detecting cardiac ischaemia is produced in all conditions where there is formation of free radicals.6 According to a study conducted by Piva S.J.et al, IMA can be an oxidative stress marker.[14] However, very few studies have assessed IMA as an oxidative stress marker in obesity. Hence, the present study was conducted to evaluate the levels of IMA in obesity and its correlation with BMI and MDA and predict the possible role of IMA as an oxidative stress marker in obesity.

In the present study the IMA levels were significantly raised in both the overweight and obese. IMA was also positively correlated with BMI. Piva SJ, et al. (2011)[14] in their study also found a significantly elevated IMA levels in overweight and obese group. A significant correlation between IMA and BMI was also noted.

These findings imply that higher IMA levels may indicate a sub-clinical condition characterized by decreased tissue perfusion and low grade inflammation wherin there is modification of serum albumin through the formation of ROS and free fatty acid.[9,15] Obesity is associated with oxidative stress and thus formation of free radicals. It is also seen that there is elevated free fatty acids (FFA).12 It is a known fact that HSA is the primary binder of fatty acids.[16]

The fasting blood glucose values were highly significantly elevated in both overweight and obese group as compared to the control normal group supported by other studies.[14] We also found a significant positive correlation between fasting glucose and IMA .Hypergly caemia leads to formation of advanced glycation end-products formed from proteins, lipids and nucleic acids. These bind to the specific cell surface receptors and form ROS through post receptor signalling.[12]

In the present study the plasma malondialdehyde (MDA) levels were also highly significantly raised in the overweight and obese group in comparison to the control group pointing towards increased oxidative stress with increased BMI. Malondialdehyde is commonly used to assess lipid peroxidation which is seen in enhanced oxidative stress conditions.[12] Olusi SO et al.[11] in their study predicted the independent role of obesity in plasma lipid peroxidation. Piva SJ et al.[14] also in their study found a significantly higher MDA levels in obese group. IMA levels were also significantly positively correlated with plasma MDA level. No study showing such a correlation could be found in obese as such. Thus it was apparent that plasma IMA level increased in the presence of increased oxidative stress as indicated by the level of MDA which is an established marker of oxidative damage.

In our study, we found that the mean values of triglyceride was significantly elevated in the overweight and obese group as compared to the control. Oxidative stress in obesity may be due to the metabolic role of increased intracellular triglycerides. The increased number of lipid molecules present in obesity may lead to their increased oxidative modification by ROS.[12] It was observed that there was no significant positive correlation between IMA and triglyceride, TC, LDL-C. However there was significant negative correlation of IMA with HDL-C. A significant negative correlation with HDL-C could imply that lower IMA can be associated to less risk of cardiovascular risk disease in obese. Only the finding of HDL-C was consistent with other similar studies. The correlations of IMA with other lipid profile parameters were not in agreement with the findings of other studies based on obesity.[17].

Hyperglycaemia, dyslipidaemia with high serum total cholesterol and TG level, besides inflammation via oxidative stress results in hypoxia with consequent modification of albumin level generating IMA. IMA is associated with excessive protein oxidative stress & protein oxidation & may indicate underlying subclinical disease.

Conclusion

1) The positive correlation between IMA and MDA in obese indivi duals suggest that IMA also can also be a good biomarker to assess oxidative stress in obesity. 2) IMA can be automated hence could be a useful technique for extensive population based studies, if so contemplated.

Limitation of the study – to prove IMA as an oxidative stress marker, the study needs to be repeated in larger group of individuals.

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