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RESEARCH ARTICLE

Association between Obesity and Markers of Inflammation, Oxidative Stress and Neuronal Injury in Women with Non-alcoholic Fatty Liver

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Abstract

One of the most common diseases is the non-alcoholic fatty liver disease which has been linked with different metabolic syndrome, such as obesity, dyslipidema, hypertension and diabetes. The present study is carried out to determine the association between obesity, inflammation, oxidative and neuronal markers with NAFLD in women. Nuclear Factor (NF)-κB, oxidized low density lipoprotein (o-LDL), total antioxidant capacity (TAC), neuron-specific enolase (NSE) and CD4 in obese women with non-alcoholic fatty liver (NAFLD). A total of 36 NAFLD obese women were enrolled in this study and 36 female control healthy women (aged 30-39) without cognitive impairment were examined. NAFLD patients were diagnosed by magnetic resonance elastography. Biomarkers of anthropometric such as height, weight, waist circumference (WC) and % of body fat were determined. Serum NF-Kb, TAC, CD4, o- LDL and NSE were measured by ELISA. Also, liver function tests, lipid profile were done. The present results showed marked elevation in serum NF-κB and o-LDL, while significant reduction in TAC and CD4 in obese NFALD than normal control subjects. In conclusion results provide evidence of association between obesity, high levels of oxidative stress, inflammatory markers and brain biomarker in women with NAFLD. The result suggests that these biomarkers may be used as potential predictors of NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a marked problem of health trouble and regarded as the greatest popular form of chronic hepatic diseases [1]. The occurrence of NAFLD parallels the elevation in the obesity rates, and exhaustion of saturated fat is positively linked with the NAFLD risk. Clinico-pathologically, NAFLD includes a wide forms of hepatic injury extended from unexciting steatosis (NAFL) to non-alcoholic steatohepatitis (NASH), fibrosis and finally cirrhosis [2].

Unexciting or bland steatosis is benign whereas NASH is described as hepatocyte lesion, where inflammation is caused by the of elicitation TNFα [3]. NAFLD pathogenesis is not completely known, and the markers that participated in the disease development are still unclear. Previous studies provided that NAFLD progression is highly linked with inflamed white adipose tissue (WAT), resistance of insulin and high levels of specific circulating meditators of inflammation as adipokines and lipids[4].

Further, studies on rats indicated that high-fat diet(HFD)-stimulated inflammatory genes in WAT introduce NASH progression in different obesity patterns, speculating a great effect of inflamed WAT in advancement of NAFLD [5]. Also, the intensity of the pathology of NAFLD shows to be closely connected to dysfunction of WAT, that is summarized as adipocytes hypertrophy joined with infiltration of macrophage, crown-like structures (CLS)formation and expression of high levels of genes of inflammation [6].

WAT is consists of various depots, which are believed to have distinct role in storage of energy and inflammatory process [7] and may thus have several involvements to the NAFLD pathogenesis. The tentative inflammation development (such as formation of CLS) in depots of WAT has not been examined and it is unclear whether a specific depot is more susceptible to become inflamed in obesity stimulated by HFD.

One of the highly active metabolic organ is the adipose tissue , so, it might be logically to suggest that fat of abdomen is well contributed to oxidative stress production, which in turn accountable for oxidation of LDL which is known to have a definitive function in atherosclerotic injury generation [8].The development of obese /and or diabetic atherosclerosis requires complicated interactions between the altered low-density lipoproteins (LDL) and the arterial wall cells. LDL and intermediate density lipoprotein (IDL) stimulated the MCP-1 mRNA expression in cultured endothelial cells of human, likely through NFκB pathway activation.

The transcription factor; NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) encourages the genes expression implicated in inflammation. Cytokines and pathogen-associated molecular patterns (PAMPs), induce toll-like receptors (TLRs) to start cascade of signaling producing NF-κB activation. NF-κB initiates high levels of genes that target to induce proliferation of cell and liberation of cytokines stimulating the response of immune system [9].

Indeed, current reports have detected the potential effect of the signal pathway of NF-κB in the hepatic and adipose tissues in the progression of inflammation-linked various metabolic disorders. Beside to, their effect in resistance of insulin in hepatic and adipose tissue, signaling pathways of proinflammation adjusted by NF-κB also participate to disease of vascular tissue connected with excess of metabolic pathwas. Oxidized lipoproteins elicited chemokines MIP-1α and MCP-1 secretion by vascular

endothelial cells, inducting leukocytes to the inflammation site [10]. NF-κB detection in macrophages nuclei in lesions of atherosclerotic vessels [11] proposed that activation of NF-κB is linked with atherogenesis. Additionally, T-lymphocytes may cooperate, with monocytic leukocytes to adjust responsiveness of insulin during obesity initiated by HFD. The lymphocytes control the differentiation and activation of macrophage by IL-6 and TNF-α generation.

Adipose tissue in obese subjects contains high level of CD8 cytotoxic Tlymphocytes and TH1-type helper CD4 T-cells, while depletion in CD4+CD25+ organized T-cells was detected [12]. IFNγ-stimulating TH1 CD4 helper T-cells infiltrate adipose tissue of mice

on HFD, speculating that T cells elicit inflammation conducting obesity and metabolic disorders. On the other hand , total antioxidant capacity is considers as the accumulative activity of all the antioxidants found in plasma and body fluids [13].

Previous studies have showed that fat accumulation and obesity are joined with chronic inflammatory process and elevation of oxidative stress (OS). Obesity stimulated by HFD has been illustrated as a crucial marker for neurodegeneration, [14].

Studies of neuro imaging have specified atrophy in cerebral cortex paralleling with high index of body mass (BMI) utilizing resonance of magnetic image (MRI) and computerized tomography. In order to explain whether obesity-linked atrophy of brain could be illustrated by injury of brain, we introduce the determination of serum levels of neuron-specific enolase (NSE).

NSE is initially found in the neurons cytoplasm and not release. Hence, this biomarker can be utilized as an efficient factor determined the neuronal degeneration. The high levels of serum NSE have been noticed in traumatic brain damage patients'. Previously, it was examined the relationship of metabolic syndrome associated brain damage, and the linkage between blood pressure (BP), blood glucose and serum level of NSE[15,16]. In this study, we proposed that the high BMI may be connected with the high NSE levels in serum [17]. Previous studies suggested that increased activity of NSE in blood cells and oxidative stress markers may be related to liver injury [18].

The present study, we aimed to study the relationship between obesity, ox-LDL, TAC, CD4, NF-κB and NSE in NFLD obese women compared to normal control one.

Subjects and Methods

120 healthy premenopausal women were subjected to the present study (60 obese and 60 non- obese). All subjects fulfilled the following criteria before study enrollment; no chronic health problems; especially; history of cardiovascular, metabolic, or respiratory diseases and depression), no history of smoking, no pregnancy. Venous blood samples were obtained. Subjects were grouped into two groups according to fat% and BMI. Subjects with BMI ≥25 kg/m^2 and body fat > 35% were placed into the obese group, and those who had <35% body fat and BMI <25kg/m^{2}were placed into the non-obese group.

Ethical Approval

This research was approved by the Ethical Committee of NRC (No: 16361) and followed the World Medical Association's Declaration of Helsinki. Furthermore, each participant in the study signed a written consent after a full description of the study.

Anthropometric Assessment

The anthropometric measurements and instruments followed the International Biological Program (IBP). Measurements were taken three times and the mean values used in the analysis included weight and height. Body weight was measured to the nearest 0.1 kg and height was measured to the nearest 1mm and BMI in kg/m^2 was calculated. Body composition was carried out using a body composition analyzer TANITA SC–330 (Tanita Corporation, Tokyo, Japan). BF% was estimated to the nearest 0.1%. Additionally, sum of skin folds (SF) including; triceps, biceps, supra iliac, subscapular and abdominal skin folds and mid upper arm circumference (MUAC), waist circumference (WC) and hip circumference were measured and waist to hip ratio (WHR) was calculated.

Biochemical Investigations

Venous blood samples were collected by direct venipuncture after an overnight fast (minimum 12 h). Quantification of MCP-1, BDNF, TNF- α and IL-6 were measured in the serum using a commercially available ELISA kit (Glory Science, Del Rio, TX, USA). The kit uses a double antibody sandwich enzyme linked immunosorbent assay. Fasting plasma glucose was measured by enzymatic colorimetric methods using a Hitachi auto-analyzer 704 (Roche Diagnostics, Switzerland) [15] and serum insulin concentration was analyzed by chemiluminescent immunoassay (Immulite 2000, Siemens, Germany) [16]. Insulin resistance has been estimated by the Homeostasis Model Insulin Resistance (HOMA-IR);as the outcome of fasting plasma insulin level (IU/mL) and fasting plasma glucose level (mmol/L) divided by 22.5 [17].

Diagnosis of Patients with Nonalcoholic Fatty Liver

A total of 36 NAFLD obese women were enrolled in the study and 36 control normal weight healthy women in matched age(aged 30–39) without cognitive impairment.This study was conducted between February 2017 and March 2018 in the National ResearchCentre, Egypt; Medical Research Centre of Excellence. The study was approved by the Ethical Committee form of National Research Centre, Egypt (number = 16361), in accordancewith the World Medical Association's Declaration of Helsinki

Results

Data in Table 1 shows comparison of clinical and biochemical characteristics between obese women with NAFLD and controls. Significant increase of obesity measures, fasting glucose, serum lipid and liver enzyme levels (AST and ALT) as compared to controls.

Table 2 shows significant increase in the serum NF-κB, O-LDL and neuromarker NSE compared to control subjects. However, CD4 and TAC showed marked reduction in NAFLD obese subjects compared to normal one.

Table1: Characteristics of obese women with NAFLD and controls

Characteristics	NAFLD	Controls
Age (year)	32.4 ± 4.7	31.4 ± 4.5
BMI(Kg/m2)	35. 25 ± 4.80**	22.21 ± 3.2
WC (cm)	93.89±10.00*	81.7 ± 4.2
Body fat %	39.7 ± 5.87*	26.5 ± 3.4
Fasting glucose (mg/dl)	100.90 ± 6.10*	81.5 ± 10.6
Total Cholesterol (mg/dl)	190.0 ± 10.0*	118.9 ± 21.1
Triglycerides (mg/dl)	157.0 ± 8.0*	104.2 ± 12.8
HDL-cholesterol (mg/dl)	35.10 ± 3.9*	49.84 ±13.7
LDL-cholesterol (mg/dl)	109.2 ± 9.43*	114 ± 9.7
AST (U/L)	56.90 ± 4.87**	25.5 ± 7.2
ALT(U/L)	70.00 ± 4.98**	23.4 ± 6.9

*p <0.05, ** p<.001 vs. controls; Data are presented as mean ±SD; BMI, body mass index; WC, waist circumference

Table 2: Different biomarkers level in serum of *NAFLD and controls*

Markers	NAFLD	Controls
NF-κB (ng/ml)	76.00±4.00**	31.00±1.98
O-LDL (mg/dl)	17.98±1.90**	4.3±0.87
NSE ug/ l	15.63± 0.22**	5.51± 0.01
CD4 U/ ml	16.9±0.54*	28.80± 0.55
TAC mmol/L	265.0±16.03**	383.63±12.11

TAC: Total antioxidant capacity; NSE: neuron-specific enolase; O-LDL: oxidized LDL

Discussion

The present study showed significant increase of serum NF-κB levels in NAFLD compared to control subjects. This may be discussed based on NF-κB transcription factor stimulate genes expression contributed with inflammation. Cytokines and pathogen-linked molecular patterns (PAMPs) induce receptors of cell surface as toll-like receptors (TLRs) to induce cascade signaling producing NF-κB activation. NF-κB in turns stimulates target genes expression that elicit proliferation of cell and liberation of antimicrobial molecules and cytokines to stimulate the response of immune system [10].

Recent researches declared a principal role for the signaling pathway of NF-κB in the hepatic tissue and adiposity, as well as

central nervous system in the progression of inflammation-linked metabolic disorders.

The possible mechanism is the binding of receptors of Toll-like on adipocytic cells or macrophages by lipids diet leading to various signaling pathway of inflammation to stimulate NF-κB resulting in several mediators of inflammation**.** The IKK kinase (IKKε) was found to be needed for high fat diet [23]. IKKε is not transcriptionally stimulated in most resting cells, but is enhanced by NF-κB stimuli. IKKε participate with NF-κB transcriptional activity in interferon signaling, and so is required to fighting specific infections of virus [24]. Expression of IKKε is upregulated 40-fold in the presence of excess of nutrient, in adipocytes and fat-infiltrating macrophages [23].

Deficiency of IKKε or differentiate obesity from high fat diet by enhancing usage, of energy, respiration of oxygen, and thermogenesis. Activation of NF-κB by excess nutrition also produces from discovery of extracellular triggers of inflammation. Deficiency of TLR4 uncoupled excess of lipid and HFD from signaling of inflammatory response in adipocytes, insulin resistance and glucose intolerance [25,26].

NAFLD obese subjects showed also, high serum levels of O-LDL which is discussed as an independent risk factor for atherosclerosis because of its associations with oxidative stress and inflammation[27]. The ox-LDL marker was highly associated with metabolic syndrome (MS) .The alteration in ox-LDL, may perhaps cause by other causes than obesity, which is its connection with variations in metabolic markers. Thus, we proposed that ox-LDL could be a promising cardiometabolic marker before insulin resistance appearance.

In particular, the abdominal fat accumulation, which can be measured indirectly through waist circumference (WC), is a critical risk factor in coronary artery disease (CAD). This is may be related to its contributions with a spectrum of metabolic disorders such as diabetes, hypertension, and dyslipidemia [27]. LDL oxidation of is consider a hallmark of atherosclerosis progress [28]. CAD patients have high level of oxidized LDL (ox-LDL) in plasma, which are joined symptoms severity and CAD degree [29].

The few studies that used circulating ox-LDL to determine oxidative stress stimulated by obesity have shown lowering ox-LDL circulating levels in obese subjects post loss of weight by surgery. However, the results regarding the relation between BMI and ox-LDL are controversial [30].

It has been shown that oxidative stress is increased by obesity [31].

Adipose tissue is considered a highly active metabolic organ, so, it might be acceptable to suppose that fat of abdomen is tightly, contributed in the oxidative stress production. The hypothesis of the current study was that indirectly measuring of abdominal fat, through WC, is independently related to circulating ox-LDL and markers of inflammation as well as in the coronary Artery Risk Development in young adults study (CARDIA), a higher ox-LDL was linked with incidence of MS elevation [32].

We investigated in the present study neuron specific enolase (NSE), a factor regarding damage of neuron, in a set of obese - NAFLD and normal subjects. There is interesting index that obesity performs a danger for density of gray matter (GM) similar to those examined for impairment of cognitive function in the elderly.

NSE is found initially in the cytoplasm of neuron and not discharged, so, this biomarker can be utilized as a good factor for examination of destruction in neuron. The elevation of serum NSE levels have been noticed in traumatic brain patients and neurodegeneration [33]. In the current study, we hypothesize that NAFLD patient with high BMI to be connected with increased serum levels of NSE.

Previous studies declared decreased Gray Matter (GM) of hippocampus correlating with elevated NSE levels in obese subject's .which is considered the first evidence linked

obesity with a particular marker of neuronal damage in brain concerning with cognitive decline. It was found that , exercise is a noticeable useful factor for cognitive function and structure of brain integrity maintenance in obese subjects –linked incline in older [34].

Further, the dramatic decrease in CD4 in serum of NAFLD obese patients may be due to decreased circulating lymphocytes production rate resulting from the diminishing in peripheral T cells , enhancement of apoptosis and no new production of T cell [27]. Previous study illustrated that ,the greatest averages weight gain was observed among patients with lower CD4 [35, 36].

Additionally ,in a high-fat diet, IFNγ-generating CD4 helper T-cells penetrate adiposity of mice [37], speculating that T cells stimulate inflammation producing obesity and metabolic disorders . The major significant result of this research is that the TAC in obese -NAFLD subjects was diminished than normal one. TAC was also decreased in obese children because they are more prone to oxidative stress [38, 39]. However, other study reported that the BMI and fate of total body were inversely correlated with TAC in diet in obesity condition [40,41].

In this study we found that TAC was decreased in NAFLD-linked obesity. Therefore it must be suggested that obese patients' consume more products of antioxidant. The occurrence of oxidative stress has been determined in children with obesity[41,42], and the oxidized LDL is linked with resistance of insulin, indepen-dent of fatness of body , and associated with the progression of resistance of insulin early in life [43].

It has been suggested that oxidative stress (OS) which is stimulated by obesity may have a role in obese pathogenesis. Several mechanisms are implicated in generating OS in obese subjects. Obesity may induce systemic OS and, in turn, OS enhanced production of adipokines, which contributes to the development of the numerous diseases [44]. Our results are also consistent with the results other results found that plasma levels of TAC were markedly lower in obese women related to healthy one.

This suggests that increased adiposity leads to increased oxidative stress which in turn lowers TAC levels counteracting increased radical production. Several studies have also shown that antioxidant defense markers are lower according to the amount of body fat and central obesity.

Possible reasons for our findings might be attributable to the fact that visceral fat mass is more metabolically active compared to subcutaneous fat mass. Adipose tissue secretes various adipokines acting in autocrine, paracrine and endocrine manner.

Excessive storage of adipose tissue, specifically in the abdomen, leads to disturbances in adipokines secretion.

This promotes endothelial dysfunction and chronic low grade pro-inflammatory state leading to numerous diseases. In physiological and, pathological conditions, adipokines induce the production of ROS, thus generating oxidative stress. However, the hypothesis that visceral fat mass alone contributes to decrease in total antioxidant capacity is not valid , but rather the total fat mass and body mass index as measures of overall adiposity.

It has been shown that the high adipose tissue content is consider the origin of cytokines of proinflammation as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1ß, and IL-6. Upon stimulation, many cells of immune response produce free radicals and, in the same way, the ROS synthesis elicited an inflammatory condition.

Obese subjects may have lower antioxidant content as a result of low intake of antioxidant or the principle antioxidant enzymes activity may be insufficient [38].

Conclusion

It could be concluded that, NF-κB activation by obesity in NAFLD subjects in which results from extracellular inflammatory triggers by classical inflammatory pathways**.** Marked reduction in CD4 cells in NAFLD obese patients speculating that T cells stimulate inflammatory response producing obesity and metabolic disorders. Our data can thus be explicated as a confirmation of the neuronal injury associated with elevated NSE marker linked with NAFLD obese subjects which could related to the specific brain regions, that contain cognitive function,

induce neuro-degeneration, O-LDL high level, suggesting that oxidative stress stimulated by obesity may have a function in obesity pathogenesis.The disruption of oxidant and antioxidant balance may be related to TAC diminishing in NAFLD obese

subjects. Further studies should also be conducted to examine the useful role of dietary consumption of antioxidants in these cases.

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