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RESEARCH ARTICLE

Association between Inflammatory Markers, BDNF, MCP-1 Levels and Insulin Resistance in Obese Premenopausal Women

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Abstract

The present study deals with the investigation of serum TNF-α, IL-6, brain derived neurotrophic factor (BDNF), monocyte chemo-attractant and protein1 (MCP-1), fasting glucose and serum insulin levels of apparently healthy Egyptian premenopausal obese women and compared with healthy non obese control women. This study aimed to determine assoction between inflammatory markers, BDNF, MCP-1, obesity measures and insulin resistance (IR) risk. The study included 120 apparently healthy Egyptian women, 60 obese and 60 non- obese. IR has been estimated by the Homeostasis Model Insulin Resistance (HOMA-IR). Results showed marked elevation in inflammatory markers and MCP-1 in obese women than controls. Significant reduction of BDNF levels was observed in obese cases with significant negative correlations with obesity measures and HOMA-IR and positive relations with TNF-α and MCP-1. In conclusion our data demonstrated increase of inflammatory markers and MCP-1 as well as decrease of BDNF levels in obese women, suggesting that these biomarkers might be positional candidate linking obesity markers that play important role for development of IR in apparently healthy Egyptian obese premenopausal women.

Keywords: *TNF-α, IL-6, Brain derived neurotrophic factor, MCP-1, Obesity, Insulin resistance.*

Introduction

Obesity is known by dramatic increase in body fat ratio to whole lean body mass causing undesirable health effects [1]. Nowadays, obesity is one of the most common health problems worldwide and its prevalence is rising in both developed and developing countries due to dietary habits changes and sedentary life.

The mechanisms causing development and progression of this pathological status are under investigation. Factors controlling energy expenditure, levels of lipids and glucose and cardiovascular homeostasis are classified as a new group known as metabotropic factors[2,3]. It is synthesized mainly in neurons. It was found also in immune cells, adipocytes, endothelial cells, and monocytes and it can be assessed in brain and blood.

This protein and its gene have been related to eating disorders and metabolic syndrome. Recent studies suggest that BDNF plays an important role in regulating energy homeostasis and body weight [4]. BDNF has not only a neurotrophic action, but also it plays a role in inflammation, metabolism and cardiovascular diseases [5].

This explains the strong interactions between brain, immune system, and adipose tissue in causing cardio metabolic diseases[6] . Moreover, it has been proved that hypothalamic decrease of BDNF alters energy homeostasis by inducing anorectic

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signal and decreasing food intake[7].Studies in animals have shown that mice with only one functional BDNF allele exhibited a tendency towards obesity [8].

Missense mutations in its receptor, TrkB, are accompanied with hyperphagia, weight gain,and obesity both in human and in mouse models [9]. In addition, administration of both exogenous BDNF and BDNF gene transfer in obese mouse model of type 2 diabetes mellitus regains normal food intake, promoting loss of weight and lowering insulin resistance [10].This suggests that BDNF insufficiency in the brain promotes obesity [11,12].

Most of the obese adipose tissue cytokines such as tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) are produced by macrophages[9]. Monocyte chemo-attractant protein 1 (MCP-1) which is one of the chemokines, has been detected in many diseases known by monocyte infiltration[13] . It is produced by many cells including, endothelial cells, monocytes, and smooth muscle cells) due to inflammatory stimuli [14].

This cytokine was newly found in cultured human adipocytes. Although in vitro studies reported that MCP-1 may participate in the occurrence of insulin resistance and stimulate differentiation of adipocytes [13], little is known about MCP-1 effect in obesity and the occurrence of insulin resistance in human. The purpose of this study is to assess the relationships between obesity, inflammatory markers (TNF-α and IL-6), BDNF and MCP-1 levels in premenopausal women

Material 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].

Results and Discussion

Results

A total of 120 apparently healthy women (60

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obese and 60 non- obese) participated in this study. The anthropometric parameters of the studied subjects are shown in (Table 1). The mean BMI, MUAC, waist circumference, waist to hip ratio (WHR), sum of SF and fat %were significantly greater in obese subjects compared to normal weight subjects (p>0.05). Table (2) presents the comparison of biochemical variables between the two groups.

In obese women serum TNF-α, IL-6 and MCP-1 concentrations were significantly higher (p< 0.001) compared with the control group, while BDNF level was significantly lower comparing with the non-obese subjects. Table (3) shows correlations between biochemical variables. Significant positive correlation was found between the inflammatory cytokines, and MCP-1 and BDNF in our cases. Table (4) shows correlation of inflammatory cytokines, BDNF and MCP-1 levels with age, BMI, body fat% in our cases. Significant positive correlations were found between serum levels of TNF-α, Il-6 and MCP-1and BMI and body fat%, while there was significant inverse correlation of BDNF with BMI and body fat%.

Table (5) shows significant positive correlation between all measured biomarkers and WC and WHR ,while MUAC showed significant correlation only with MCP1 ($p \leq 0.05$), on the other hand TNF-α and MCP-1 showed significant positive correlation with sum of skin folds ($p \leq 0.05$) and BDNF showed significant negative correlation with waist, WHR and HOMA-IR.

Table 1: Anthropometry and body composition of obese and non-obese women

Characteristics	Obese	Non-obese
Age (years)	31.2 ± 4.4	32. 1 ± 4.5
BMI(kg/m²)	31.24± 5.7**	22.24±3.2
MUAC(cm)	35.5± 8.1*	24.9± 4.7
WC (cm)	99.2± 8.15**	80.4 ± 4.2
WHR	0.85± 0.08*	0.73± 0.06
Sum SF (mm)	148. 5 ± 22.9*	130.1 ± 21.2
Body fat%	37.8±9. 6*	23.5±8.4
HOMA-IR	4.5 ± 2.5	3.2 ± 1.4

BMI: body mass index; Sum SF: sum of skin folds; MUAC: mid upper arm circumference; Data are presented as mean± SD, *p<.05, ** p<.001

Table 2: Comparison between inflammatory markers, BDNF and MCP1 in obese and non-obese women

Biomarker	Obese	Non –obese	P
TNF-α(pg/ml)	27.12±2.76	12.45±1.16	0.001
IL-6(pg/ml)	6.00±2.00	1. 85±0.80	0.001
BDNF (ng/ml)	13.12±1.21	25.20±3.11	0.001
MCP-1 (pg/ml)	266.00±10.00	90.62±12.00	0.001

Data are expressed as mean ± SD

Table 3: Correlations between inflammatory cytokines, BDNF and MCP-1 in obese women

Biomarker	TNF- α		IL-6		BDNF		MCP-1	
	r	p	r	p	r	p	r	p
TNF-α (pg/ml)	-	-	0.84	0.001	0.56	0.01	0.55	0. 01
IL-6 (pg/ml)	0.84	0.001	-	-	0.312	0.05	0.55	0. 01
BDNF (ng/ml)	0.56	0.01	0.312	0.05	-	-	0.53	0. 01
MCP-1 (pg/ml)	0.55	0. 01	0.55	0. 01	-0.53	0.01	-	-

Table 4: Correlation of inflammatory cytokines, BDNF and MCP-1 levels with age, BMI, body fat% in obese women

Biomarker	Age		BMI (kg/m²)		Body fat%	
	r	p	r	p	r	p
TNF-α (pg/ml)	0.15	0.198	0.84	0.001	0.86	0.001
IL-6	0.16	0.198	0.83	0.001	0.84	0.001

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(pg/ml)						
BDNF (ng/ml)	0.15	0.198	-0.85	0.001	-0.85	0.001
MCP-1 (pg/ml)	0.14	0.198	0.87	0.001	0.88	0.001

BMI: body mass index; TNF – α: tumor necrosis factor; IL-6, interleukin-6; BDNF: Brain-derived neurotrophic factor; MCP-1, monocyte chemoattractant protein-1

Table 5: Correlation of inflammatory cytokines, BDNF and MCP-1 levels with MUAC, WC, WHR, sum SF and HOMA-IR in obese women

Biomarker	MUAC (cm)	WC (cm)		WHR		Sum SF (mm)		HOMA-IR	
	r	p	r	p	r	p	r	p	r	p
TNF-α (pg/ml)	0.12	0.18	0.46	0.01	0.58	0.01	0.350	0.05	0.56	0.01
IL-6 (pg/ml)	0.13	0.198	0.44	0.01	0.60	0.01	0.111	0.176	0.47	0.01
BDNF (ng/ml)	- 0.12	0.188	- 0.45	0.01	- 0.34	0.05	- 0.13	0.180	- 0.57	0.01
MCP-1 (pg/ml)	0. 38	0.05	0.82	0.001	0.88	0.001	0.32	0.05	0.79	0.001

Discussion

In the current study, we found that obese women had significant lower serum levels of BDNF compared to normal weight women. These results are consistent with previous studies that reported lower levels of serum BDNF in obese subjects compared to those with normal weight [18,19] . Moreover, we detected significant negative correlation between serum BDNF and body fat % in our cases. On the contrary to our results, other study detected higher BDNF serum concentrations in obese children than those with normal weight thus suggesting an association between BDNF and fat mass [20].

Parallel to our results are the studies declared that obesity is associated with decreased serum levels of BDNF, and returning its normal functional concentrations by giving BDNF might stop the metabolic syndrome harmful outcome[6]. On the other hand, our results disagree with those of [2,21] who found that serum BDNF level in obese women was not significantly different from those of normal weight women. They also found negative correlation between BDNF and WHR which was considerable but not statistically significant, (p= 0.06).

In this context, we detected significant negative correlation between BDNF and WHR (P< 0.05). In fact, there are debatable outcomes from past researches which demonstrated that serum levels of BDNF in obese females were similar to its levels in normal weight cases. In this aspect, previous study [22] stated that serum levels of BDNF in metabolic syndrome cases are not different from normal controls[21]. In this regards also previously [23] in a meta-analysis study, concluded that, obese cases have BDNF levels parallel to those of controls and obesity is most likely not accompanied with decreased serum BDNF levels.

Additionally, a previous study[24] reported that the serum level of BDNF was not different in the studied cases, concerning obesity and concluded that obesity has no effect on the level of BDNF. They reported that no correlation was found between body weight and BDNF serum level. These results are in contrast with our results as we detected significant negative correlation between BMI and serum level of BDNF. Actually, the influence of BDNF as anti-obesity factor has been proved [25]. In addition, subjects having BDNF gene mutations present with marked obesity [26]. Accordingly, decrease serum BDNF level in obese subjects is rather reasonable.

Contradictories in the results of many studies could be due to alteration in degree of obesity of investigated cases. For example, the researches that exhibited decrease BDNF levels were on children and marked obese cases[18,19] , while other work which declared elevated BDNF levels in obese cases, was done on children in early period of obesity (overweight) who were matched with incompletely normal weight children (BMI was 28.9 vs. 18.9 kg/m^2)[20].

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The neurotrophic hypothesis proposes that neurotrophins play an altered role in metabolic diseases early or late stage. It has been supposed that levels of neurotrophin are elevated in initial stage of metabolic disorders to counteract and reduce evolving inflammatory condition. However, once metabolic syndrome criteria are established, neurotrophins levels start to decrease progressively due to effect of proinflammatory cytokines on the neurotrophins. Consequently, a hyponeurotrophinemia occurs in the advanced diseases stage [27] this may be a good explanation to our results.

It is evidenced obviously by many studies that abdominal obesity is accompanied with the inflammatory cytokines production[28]. This coincides with our results which showed highly significant increase of serum IL-6 levels in obese women than in normal weight ones with positive correlation of IL-6 with both WC and WHR. Our findings are in agreement with those of other studies [24] who concluded that the concentration of interleukin-6 was significantly higher in obese women than lean ones.

Interestingly, our study revealed correlation of IL-6 and BDNF which is inconsistent with the results of the study done previously [24], who detected no correlation between serum level of IL-6 and BDNF. However, many authors demonstrated this correlation[29]. It is clearly evident that adipose tissue secretes many proinflammatory cytokines which are in direct proportion to adiposity.

These include, TNF-α, IL-6and MCP-1 which have been involved in the occurrence of harmful effects concomitant with obesity [30]. TNF-α plays a role in the development of obesity-induced insulin resistance [31].TNF-α and IL-6 also induce lipolysis and have been involved in the hypertriglyceridemia associated with obesity. Macrophage accumulation in relation to adipocyte size may induce the adipose tissue secretion of these proinflammatory and therefore participate in the pathophysiological complications of obesity [1].

The previous findings are supportive to our results which detected significantly higher level of TNF-α and IL-6 in obese females than in lean ones. In addition, we found significant positive correlation of serum levels of TNF-α, Il-6 with BMI, body fat %, WC and WHR. Obesity is known by an extensive inflammatory reaction. Macrophage infiltration in adipose tissue of obese subjects is characteristic, and elevated levels of MCP-1 in response to TNF-α would maintain this inflammatory response[32].

Coinciding with this are our results which demonstrated significant positive correlation between serum levels of TNF-α and MCP-1in our cases. High MCP-1 plasma level has been detected in obese subjects compared to lean controls[33]. It correlated with visceral adiposity[34] as detected in a previous study. The circulating MCP-1 high levels in obese persons were more elevated by fructose intake , decreased by low-glycemic index food [35].

Moreover, MCP-1 signaling has a strong influence in the occurrence of obesity through its angiogenic effect on endothelial cells and thus it can participate in the enlargement and conversion of adipose tissues [36]. Actually, these are coinciding with our results which indicated highly significant increase of MCP-1 serum level in obese women compared to the lean ones. There was also significant positive correlation between serum level of MCP-1 and serum levels of IL-6, TNF-α and BDNF.

Additionally, we detected significant positive correlation between MCP-1 and all the anthropometric measures of adiposity including BMI, fat mass, and WC, WHR, MUAC and skin fold thicknesses. Compatible with our findings, the results of the study done by [37] reported a positive correlation between MCP-1 expression and BMI in non- diabetic subjects.

Moreover, previously, many researchers have reported an association between MCP-1 adipose expression and circulating levels of MCP-1;proposing that adipose tissue could be a significant provider to plasma MCP-1 levels [35,38]. However, other studies [37,38] did not confirm this observation; as they declared that circulating MCP-1 levels showed no direct correlation with adiposity; in agreement with a previous report in which the secretion of MCP-1 from adipose tissue to peripheral circulation was similar in obese and in lean subjects and was not affected by sex, age, and homeostasis model assessment of insulin resistance index [37]. Nevertheless, they could not reject an association between

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visceral adipose tissue content and plasma MCP-1 levels. Other study[37] declared a positive correlation between WHR and circulating MCP-1 in non-diabetic subjects($p = 0.04$). Indeed, this is in concordance with our results.

The current study demonstrated that the MCP-1 serum levels were significantly higher in obese subjects compared to non-obese controls and were positively correlated with the parameters of obesity including; BMI, body fat%, WC and WHR , MUAC and sum of skin folds thickness. Thus our findings suggest that body adiposity may affect the serum levels of chemokines such as MCP-1 and IL-6. Previously, several studies have demonstrated that MCP-1 is released by adipose tissue and rises with more fat mass in obese persons [39].

Therefore, it was found linking of these cytokines particularly to the occurrence of obesity and its complications. The same results were found by the previous study [40]. They observed an association between MCP-1 serum levels and BMI and detected that the MCP-1 serum levels were significantly increased with increasing waist circumference, indicating that visceral fat can contribute to rising of MCP-1 serum level in obesity [40].

Supporting our results; they also found that the levels of MCP-1 were positively related to the level of IL-6 in obese cases.

Conclusion

Obesity is associated with increase of inflammatory markers as indicated by elevation of IL-6, TNF-α and MCP-1 and decreased of BDNF levels that might link with IR risk in obese women.

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