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The Effect of Body Weight Gain with or Without Diabetes Type 2 on the Levels of Noradrenalin and Some Neurotrophins

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Abstract: *This work aimed to study the effect of body weight gain in individuals with or without diabetes mellitus Type 2 (DMT2) on the nervous system. Seventy-five subjects participated in this study, including 25 obese patients with DMT2 (BMI≥30kg/m^2), 25 obese individuals without diabetes (BMI≥30kg/m2) and normal-weight healthy (BMI<25kg/m^2). In addition to body mass index (BMI), the west/hip ratio (WHR) and total body fat (TBF%) were calculated. 10ml of blood was collected from participants and used to determine the levels of HbA1C, noradrenaline (NA), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and fasting blood glucose (FBG). The level of NGF increased while BDNF and NA levels decreased in obese with and without diabetes compared to control. Interestingly, BDNF level was significantly higher in the obese with diabetes than without. Moreover, TBF% and WHR values were significantly higher in the obese with diabetes when compared with those without diabetes. At the same time, there were no significant differences between BMI value in these two groups. BMI, TBF% and WHR significantly correlate with FBG, HbA1C and NGF and negative significant correlation with BDNFdoes not correlate; only WHR has no correlationdoes and does not correlate with NA. As well as, HbA1C has a significant correlation with the nerve markers, positive with BDNF and NGF and negative with NA, while FBG did not correlate with them. In conclusion, neurotransmitters and neurotrophin levels could use as risk factors for diabetes, and obesity could be considered as a risk factor for neuropathy as much as diabetes.*

Keywords*: *BMI, diabetes, obese, NA, BDNF, neurotrophins

1. Introduction

Obesity is an abnormal or excessive accumulation of fat that can harm one's health [1]. It can be brought on by a disruption in the regulation of food intake, which causes an increase in energy intake relative to the body's

metabolic needs and, as a result, a rise in energy intake relative to energy expenditure and weight gain [2]. About 1.9 billion people aged 18 and older were projected to have an estimated prevalence of overweight and obesity in 2016, with over 650 million of this group being obese [3].

Since it is the only body measurement that directly estimates an individual's relative body composition without considering a person's height or weight, total body fat percentage is one of the most helpful markers for evaluating overweight and obesity. A measurement that enables comparison of the adiposity of individuals of various heights and weights is the commonly used body mass index (BMI) [3].

Due to differences in body composition, BMI largely increases with adiposity. However, the second measure of body fat delivers more accurate findings; for instance, those with more bone or muscle mass would have higher BMIs [4].

As such, BMI is an accurate measure of fitness for a large group of individuals, but it is a poor tool for evaluating an individual's health. Another marker for obesity is the waist circumference or waist-to-hip ratio (WHR), which can better describe the amount of intra-abdominal fat and maybe a better indicator of the risk of developing numerous illnesses, including diabetes, than BMI [5].

The time it takes for obesity to develop, the total amount of body fat, and the distribution of fat in the central region of the body are all warning signs that T2DM may be on the way [6]. In this regard, it comes to light that 80% or more of the patients are obese. This is explained by the recently discovered fact that adipose tissues are neither inert nor restricted to serving as an energy storage organ but instead are a major endocrine organ and play a substantial role in the etiology of T2DM and insulin resistance (IR) [7].

Diabetes mellitus is a group of various metabolic disorders, including abnormalities in carbohydrate, lipid, and protein catabolism and anabolism, which usually appear as hyperglycemia and glucose intolerance due to insulin deficiency, insulin resistance, or both [8].

The maintenance of glucose and energy balance depends on the central nervous system [9]. Effective cerebral insulin signaling is a key regulator of these pathophysiological processes in animals and humans because neural mechanisms have been implicated in obesity and insulin resistance [10]. A key role in this intricate, bi-directional interaction has been indicated for sympathovagal imbalance and the relative predominance of sympathetic activity [10].

Insulin activity in the brain is regulated on several levels by metabolic, endocrine, and neurological signals triggered by nutrition, processed mainly by the hypothalamus. The way insulin interacts with the neuroregulatory systems that control anabolism and catabolism is particularly intriguing. The neurotransmitter serotonin, the anorexic peptides leptin and insulin, and the insulin receptor substrate, the phosphatidylinositol-3-kinase (PI3K) pathway, all share similar signaling pathways implicated in food consumption. This signaling pathway has the potential to play a significant role in the interaction between neurotransmitters and peptides that regulate eating behavior as well as the pathophysiology of the brain in general. [9].

One of the neurotrophins is brain-derived neurotrophic factor (BDNF), which plays a key role in forming neural networks, synaptic plasticity, neuronal regeneration, and neuroprotection. Diabetes and neurode - generative, neurological, or even cardiov - ascular illnesses, are linked to up- and down-regulations of BDNF levels in human blood and tissue [11].

Another neurotrophin, nerve growth factor (NGF), is generated endogenously by a variety of cell types, including neurons, Schwann cells, oligodendrocytes, lymphoc - ytes, mast cells, macrophages, keratinocytes, and fibroblasts, throughout development and

maturation. These cells generate proNGF, which the endoplasmic reticulum proteoly - tically cleaves into physiologically active NGF [12]. As a result, it plays a crucial role in the metabolism of lipids and is linked to the development of diabetic problems, obesity, and neurological conditions [13].

The hypothalamic-pituitary-adrenal (HPA) axis activation and release of arginine-vasopressin (AVP) are both dependent on the central noradrenaline (NA), one of the neurotransmitters. Although the interaction between these systems is unknown, dysregulation contributes to stress-related illnesses, including human obesity.

So, our work aimed to study the effects of body weight gain in individuals with or without diabetes mellitus type 2 on the NA and some neurotrophins, which are BDNF and NGF.

2. Methodology

This Case-Control study was achieved from November 2022 to January 2023. Body weight of the individuals with or without diabetes mellitus type 2 were measured by electric balance (Coleman, U.S.A) and their height of them by measuring tape. Then, the body mass index was calculated by divided the body weight in kilograms on the square of body height in meters [15].

The number of participants in this study was 75 subject including 25 obese patients with diabetes mellitus Type 2 (BMI≥30kg/m2) which were randomly selected from the patients that visited the private and National Diabetes Center of Mustansiriyah University/ Baghdad/ Iraq, 25 obese individuals without diabetes (BMI≥ 30kg/ m2) which were randomly selected from the visitor of private obese centers/ Baghdad/ Iraq and 25 healthy and normal weight individual (BMI<25kg/m2) which were randomly selected from students and employees in the Mustansiriyah university. Their age is ranged between 20-45 years.

The waist/hip ratio were calculated by dividing the waist circumference by the hip circumference, where both waist and hip circumferences were measured with a tape measure [16]. In addition, the total body fat percentage was calculated by using the following equation [17]:

TBF%= (1.2 x BMI) +(0.23 x age) -(10.8 x gender*)-54

*Where the female is indicated by zero and the male by the number one

By puncturing the vinous vein, 10 milliliters of blood were drawn from each participant. Eight milliliters of blood were placed in a gel tube (without an anticoagulant) and centrifuged at 3000 rpm for 10 minutes to obtain the serum, while two milliliters were placed in an EDTA tube for the direct detection of HbA1c on ichromaTM instrument testing. The serum was then kept in the freezer at -18 C until it was used to measure the levels of NA, BDNF, and NGF using the sandwich enzyme-linked immunosorbent assay (ELISA) technique using kits available commercially from ShanghaiYL Biont/China and FBG using an automatic biochemistry analyzer using the Barham and Trinder technique.

Results were reported as mean, SE, or SD. Following one-way analysis of variance (ANOVA), the data were subjected to several comparisons using Fisher's test. An analysis of combined variation (ANCOVA)-based regression analysis was performed. All of the analysis was carried out with Statview 5.0. The differences were deemed significant when p 0.05 was attained.

3. Results

Table (1) shows the difference in the FBG and HbA1c among obese with and without DMT2 and the control. The FBS levels in obese patients with DMT2 was significantly higher than in other non-diabetic Obese and average weight (control) groups (204.48±84.74, 91.95±10.20 and 94.10±6.24 mg/dl, respectively). The same result was found in HbA1c%. It was significantly higher in obese patients with DMT2 than non-diabetic Obese and control groups (8.89±1.67,

5.30±0.25 and 5.06±0.23%, respectively).

Table (1): The level of HbA1C % and FBS (mg/dl) in all groups

Groups	FBS mg/dl Mean ±SD	HbA1C% Mean ±SD
Diabetic obese	204.48±84.74*	8.87±1.67*
Obese	91.95±10.20	5.30±0.25
Control	94.10±6.24	5.06±0.23
P-value	D.O & O<0.0001 D.O & C<0.0001 O & C. <0.889	D.O& O<0.001 D.O& C<0.001 O& C.= 0.429

The data in Table (2) shows that NGF level increased in the obese with and without diabetes compared to control (11.30±0.73, 11.83±1.06 and 6.90±0.81 ng/ml, respectively). In contrast, BDNF levels decreased in them compared to control (0.250±0.028, 0.154±0.032 and 0.461±0.034 ng/ml, respectively), and NA levels also decreased in them compared to control (77.85±8.74, 87.04±8.27 and 119.27±15.75 ng/ml, respectively). Interestingly, the difference between these parameters in the obese with and without diabetes was non-significant except BDNF level which was significantly higher in the obese with diabetes.

Table (2): The levels of NA, BDNF and NFG in all groups

Groups	BDNF Ng\ml Mean ± SE	NGF Ng\ml Mean ± SE	NA Ng\ml Mean ± SE
Diabetic obese	0.250±0.028	11.30±0.730	77.85±8.74
Obese	0.154±0.032	11.83±1.060	87.04±8.27
Control	0.461±0.034	6.90±0.810	119.27±15.8
P-value	D.O&O= 0.02 D.O&C<0.001 O&C<0.0001	D.O& O= 0.6 D.O&C=0.001 O& C.= 0.001	D.O&O= 0.53 D.O&C= 0.01 O&C= 0.024

Moreover, the Total boy fat percentage (TBF%), waist-hip ratio (WHR), and body mass index (BMI) value of the three groups were shown on the table 3, all these markers were significantly higher in obese with and without diabetes compared to control. However, TBF% and WHR values were significantly higher in the obese group with diabetes (44.93±8.44% and 0.97±0.06, respectively) compared with obese without diabetes (36.63±10.77% and 0.84±0.07, respectively). At the same time, there was no significant differences between BMI value in these two groups (38.19±6.91 and 38.39±5.95, respectively).

Table (3): The levels of TBF, WHR and BMI in all groups

Groups	TBF% (Mean ±SD)	WHR (Mean ±SD)	BMI kg/m2 (Mean ±SD)
Diabetic obese	44.93±8.44	0.97±0.06	38.19±6.91
Obese	36.63±10.77	0.84±0.07	38.39±5.95
Control	23.75±6.12	0.672±0.066	23.60±3.48
P-value	D.O&O=0.04 D.O&C<0.0001 O&C<0.0001	D.O&O=0.01 D.O&C<0.0001 O&C=0.0004	D.O&O=0.91 D.O&C=0.001 O&C<0.0001

The correlation of obese markers (BMI kg/m^2, TBF% and WHR) with the diabetes markers and nervous system markers were shown in Table 4. BMI has significant correlations with diabetes markers (FBG and HbA1C) and NGF, no significant with BDNF and on significant correlation with NA while TBF% has significant positive correlation with HbA1C and NGF, negative correlation with BDNF while no significant correlation with FBG and NA. Interestingly, WHR has significant correlations with all diabetes and nerve markers. It has a positive correlation with FBG, HbA1C and NGF and a negative correlation with BDNF and NA

Table (4): The correlation of obese markers with diabetes and nerve markers

	BMI kg/m^2	**TBF%**	**WHR**
FBG (mg/dl)	P=0.007 R=0.101	P=0.140 R=0.086	P=0.002 R=0.13
HbA1c%	P=0.0002 R=0.13	P=0.0002 R=0.187	P=0.002 R=0.13
NA (ng/ml)	P=0.070 R=0.052	P=0.075 R=0.049	P=0.045 R=0.06
BDNF (ng/ml)	P=0.006 R=0.109	P=0.011 R=0.09	P=0.008 R=0.08
NGF (ng/ml)	P<0.0001 R=0.206	P<0.0001 R=0.203	P<0.0001 R=0.204

As well as the correlation of the diabetes markers with the nerve markers were shown in table 5. Interestingly, only HbA1C significantly correlates with the nerve markers, positive with BDNF and NGF and negative with NA while FBG did not correlate with them.

Table (5): the correlation of diabetes markers with nerve markers

	FBG (mg/dl)	**HbA1C%**
NA (ng/ml)	P= 0.453 R= 0.008	P= 0.0498 R= 0.044
BDNF (ng/ml)	P= 0.315 R= 0.015	P= 0.0479 R= 0.017
NGF (ng/ml)	P= 0.522 R= 0.006	P= 0.0424 R= 0.047

4. Discussion

The current result showed that the level of FBS and HbA1c is higher in obese with diabetes mellitus than both obese without DM and the control group, which agree with the findings obtained by many studies such as [18,19,20,21,22]. Diabetes mellitus type 2 with high blood glucose levels dramatically reduces insulin impact on the body because the body cells are insensitive to insulin impacts or the pancreas does not make enough insulin to maintain a normal glucose concentration. As a result, glucose builds up in the circulation (hyperglycemia) [23]. Common proteins such as HbA1c, which is often believed to reflect the integrated mean glucose level over the previous 8–12 weeks as well as being calculated by the 120-day lifespan of the erythrocyte, may get more glycated at high glucose concentrations. HbA1c is created through the non-enzymatic attachment of glucose to haemoglobin. Because it represents more detrimental glycation sequelae of diabetes, including retinopathy and nephropathy, which are known to be caused by hazardous advanced glycation end products, the concentration of HbA1c predicts diabetes problems [24,25,26].

Compared to the control group in this investigation, these results likewise demonstrated a reduction in BDNF levels in obese individuals with and without DMT2. In a Chinese population, the same findings were observed: BDNF serum levels were considerably lower in patients with type 2 diabetes mellitus than in a healthy control group, and they were also linked to diabetes risk, complications, and obesity [27]. In reality, it has been demonstrated that hypothalamic BDNF decreases regulates energy balance, influencing calorie intake and favouring an anorectic signal [28]. As well as, Hyperfagia, weight gain, and obesity have been linked to BDNF haploinsufficiency [29] or missense mutations in its receptor, TrkB [30], in both animal and human models. Exogenous BDNF administration and BDNF gene transfer in a mouse model of obesity and type 2 diabetes mellitus restored normal food intake, causing weight loss and lowering insulin resistance, which is consistent with these observations [31] and support the idea that BDNF deficiency in the brain causes a metabotropic impairment that results in obesity and type 2 diabetes [32]. This evidence could explain the negative correlation of BDNF with obese markers (BMI,

TBF and WHR) and HbA1C but not FBG, which will be described later in the discussion.

Interestingly, the body's capacity for producing naturally occurring nerve growth factors may be impacted by diabetes. Additionally, it can impair the body's capacity to return the typically occurring nerve growth factor to the nerve cell from skin tissue [33]. Therefore, among the pathophysiological causes causing peripheral neuropathy, reduced nerve growth factor levels may be crucial. In agreement with these findings, many investigations have discovered that early-stage diabetics have lower levels of nerve growth factor [34]. Earlier research has shown that people with diabetes have deficiencies in the synthesis and retrograde axonal transport of nerve growth factor produced from sympathetic and sensory target tissues [35] , which agreed with our findings in this study and explain the positive correlation of NGF HbA1C but not FBG which will be explained it later in the discussion.

On the other hand, it is well established that there is a positive correlation between NGF and disorders linked to Inflammation. NGF receptors nd their expression and synthesis in immune cells, have been reported [36, 37]. NGF has had a regulatory influence on cytokine production or mediator release and cell survival or differentiation [38]. However, Inflammation has come to be seen as one of the leading causes of obesity. NGF, on the other hand, is produced and released by white adipocytes, and a sample of obese individuals had greater levels of mRNA than normal-weight participants or people with MetSyn. These white adipocytes and immune cells might be directly responsible for obese people's elevated levels of NGF in the blood. Interestingly, since the NGF plays an important role in maintaining and guiding the neurons, especially dopaminergic or noradrenergic neurons, it has been reported that the damage of dopaminergic or noradrenergic neurons, which lead to reduced NA level may result in increased NGF level [39] which agree with our results and explain the positive correlation of NGF with the obese markers (BMI, TBF and WHR).

It is well established that the sympathetic nervous system activity is stimulated. Although the specific mechanism by which obesity occurs is still unknown, Landsberg has developed an intriguing theory that at least partially explains its occurrence. [40] His theory contends that when people overeat, the sympathetic nervous system is activated, which aids in stabilizing body weight by promoting thermogenesis at the expense of sympathetic nervous system activation in the heart, kidneys, and vascular system, which may raise blood pressure. As evidenced by a rise in whole-body noradrenaline spillover rates, overeating does enhance sympathetic nerve activity in humans [41]. This hypothesis could explain the situation in the hypertension obese individuals, but in our study, all the participants were normotension which cannot have an elevation in NA. However, whether or not adrenergic activation is a characteristic of obesity is a subject of intense debate. Increased caloric intake increased norepinephrine turnover in animals [42, 43].

However, in Zucker rats, a traditional animal model of weight gain, body weight only slightly increased, and no norepinephrine secretion was noted [44]. Studies on obese normotensive males have similarly found that their plasma norepinephrine levels are higher than those of lean control participants. Still, they might also show no change or decrease [45, 46, 47]. Because most of the norepinephrine released by the sympathetic fibres is destroyed or reabsorbed and only a small proportion escapes from the neuroeffector junctions, plasma norepinephrine is an indirect and somewhat insensitive indicator of sympathetic activity [48, 49].

The microneurographic technique, allowing for direct, accurate, and repeatable measurement of sympathetic neural discharge from the human peroneal or brachial nerves [50], can, however, get over this constraint.

Microneurographic studies have thus far demonstrated that sympathetic nerve traffic may be associated with body fat in some races [51].

This evidence could explain the decrease in the NA levels in the obese patients with or without DMT2 and its significant negative correlation with the HbA1C and WHR.

One of diabetes's long-term consequences is neuropathy. Over time, high blood glucose levels might harm the tiny blood vessels that nourish the neurons and obstruct their ability to receive vital nutrients. As a result, the nerve fibres may sustain injury [52] that alters the neurotransmitters and neurotrophins previously mentioned. As a valid indicator of chronic glycemia and a predictor of the likelihood of long-term diabetic problems [53], HbA1c significantly correlated with NA, NGF, and BDNF in our investigation.

In this study, a significant correlation of BMI with the FBG, HbA1C, NGF and BDNF but not with NA, TBF% with HbA1C, NGF and BDNF but not FBG and NA, while WHR correlates with all diabetes and obese marker. Some evidence found Some published studies [54, 55, 56, 57] found that BMI had a similar ability to predict diabetes as did WHR, despite mounting evidence that WHR had a superior ability to predict diabetes than BMI [58, 59, 60]. This is because WHR can more accurately reflect the buildup of intra-abdominal fat and maybe a more accurate predictor of the risk of type 2 diabetes than BMI [61].

Conclusion

The levels of NA, NGF and BDNF change in obese individuals and have a correlation with the obese markers; BMI, TBF% and especially WHR, which can more accurately represent the buildup of intra-abdominal fat and serve as a better indicator of the risk of type 2 diabetes.

So, neurotransmitters & neurotrophins could use as risk factors for diabetes. Moreover, from these results could be concluded that not only diabetes but also obesity could be considered a risk factor for neuropathy.

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