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TYPE 2 DIABETES MELLITUS AND OBESITY AS RISK FACTORS FOR DEPRESSION AND COGNITIVE IMPAIRMENT

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ABSTRACT

Background: Cognitive impairment and Depression were associated with diabetes has been of serious concern to physicians worldwide. Diabetes mellitus, if not managed, may increase the risk of cognitive impairment, as the cognitive behavior deteriorates faster in diabetic patients. The aim of the present study is to highlighting the relation between Type 2 Diabetes and obesity with Depression and Cognitive Impairment

. **Patients and methods:** A comparative cross sectional study was carried out on 90 adults equally divided into three groups: (A) diabetic patients with normal BMI, (B) non-diabetic individuals and (C) obese type 2 Diabetic patients. All groups were subjected to the full medical history in a positive family history of diabetes, lifestyle factors and physical activity, complete clinical examination and laboratory investigation.Cognitive impairment and Depression assessment were performed.

Results: Physical activity was significantly associated with Group A & B and hyperlipidemia associated with Group A& C**.** Our results showed group B was significantly lower regard FBS, PPS and HbA1c than group A&C with no significant difference between them . Group A was significantly lower and overall depression was significantly associated with group B and Group C as it was 30.0% and 46.7% respectively. There no significant difference founded among groups as regard cognitive impairment, Type 2 Diabetic patients groups (Group A 26.7%-Group C 33.3)% while group B (Obese non Diabetic) showed less prevalence of cognitive (13.3%).

Conclusion: Type 2 Diabetes mellitus associated with high prevalence of Depression and Cognitive Impairment. The results of this study confirm the basis for a better understanding of the association between Cognitive Impairment and depression in patients with diabetes mellitus type 2, and obesity and will allow development of prediction tools and better interventions.

Keywords: Cognitive Impairment; Obesity; Depression, Type 2 Diabetes Mellitus

INTRODUCTION

Depressive is a disorder affecting approximately 350 million people globally. The lifetime prevalence of major depressive disorder is high and could affect up to 14.6 %–20% of the population **(1).**

It has been observed that having significant symptoms of depression is common in individuals with type 2 diabetes mellitus. It has been reported that individuals with type 2 diabetes mellitus have an increased risk up to 2.0–4.71-fold of having depression compared to individuals without diabetes **(2).**

A recent meta-analysis that includes the terms “depressive disorder” showed that one in four adults with type 2 diabetes mellitus suffer depression **(3).** There is a neurobiological mechanism that may explain the bi-directional relationship between major depression or significant depressive symptoms and type 2 diabetes mellitus, which associates a dysfunction in the adrenal–pituitary–hypothalamus axis with cortisol elevations, alterations in corticotrophin-releasing hormone levels and neurotrophins **(4).**

Obesity has massively increased worldwide and it has been reported that individuals with obesity have up to 32% higher risk of having significant depressive symptoms than comparison groups **(5).**

In relation to diabetes, some studies have shown that major depression and more prominent symptoms of depression are more common in individuals with type 2 diabetes and obesity **(6,7).** As well as the association between type 2 diabetes and obesity **(8).**

Type 2 diabetes mellitus have been associated with reduced performance on numerous domains of cognitive function. The exact pathophysiology of cognitive dysfunction in diabetes is not completely

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

understood, but it is likely that hyperglycemia, vascular disease, hypoglycemia, and insulin resistance play significant roles (**9).**

In this study we aim to highlighting the relation between Type 2 Diabetes and obesity with Depression and Cognitive Impairment.

PATIENTS AND METHODS

A comparative cross sectional study was carried out on 90 adults equally divided into three groups: (A) diabetic patients with normal BMI, (B) non-diabetic individuals and (C) obese type 2 Diabetic patients who attending to the Diabetes out-patient clinic in Internal Medicine Department, Faculty of Medicine, Zagazig University Hospitals from April 2021 to July 2021. An informed consent was obtained from each patient, control or their legal guardians before enrolment in the study. This study was approved from the Local Ethical Committee of Zagazig University.

Inclusion criteria:

Obese Individuals, type 2 diabetes patients, aged 18 years and over of both gender. Type 2 diabetes patients with normal BMI (the duration of diabetes between 5-15 years and obese patients with type 2 diabetes(duration of Diabetes between 5-15 years).

Exclusion criteria:

Patients who less than 18 years old, type 1 diabetes, Incomplete Beck Depression Inventory (BDI), MOCA or clinical data, pregnancy and post menopause, Inability or refusal to provide informed consent, alcoholic and drug abuse, duration of Diabetes less than 5 years and more than 15 years.

Patients were divided equally into: Group (A): included 30 Type 2 diabetes patients non obese, Group (B): included 30 obese patients without diabetes (30) patients and Group (C): included 30 Obese patients with type 2 diabetes.

All groups were subjected to the full medical history in a positive family history of diabetes, lifestyle factors and physical activity and complete clinical examination.

All measurements were performed in the morning after 10- to 12-hour fast and in a stable room temperature of 23 ± 1°C. All individuals were asked to avoid smoking and caffeine intake for 8 to 10 hours, while antidiabetic or other medications withheld and administered to the participants at the end of the examination.

Anthropometric measurement:

Height, weight and Body mass index (BMI) were measured. Waist circumference measured at the minimal abdominal girth between the rib cage and the iliac crest.

Sample collections:

Blood samples were collected from the antecubital vein and centrifuged. The serum was taken immediately for analysis or stored at -20 °C for further use glucose levels (FBS& PPS) and lipid profile. (3ml) was collected in (EDTA) tube for HbA1c measurement. Glucose tolerance test (75g) was done for individuals without a history of diabetes and a second blood sample was obtained 2 hours after the ingestion of glucose. .

Laboratory investigations:

1. Fasting blood glucose:

Glucose reagent is used to measure the glucose concentration by a timed end point method. In the reaction, hexokinase (HK) catalyses the transfer of a phosphate group from adenosine triphosphate (ATP) to glucose to form adenosine diphosphate (ADP) and glucose-6- phosphate. The SYNCHRON CX system automatically monitors the change in absorbance at 340 nanometers. This change in absorbance is directly proportional to the concentration of glucose inthe sample and is used by the SYNCHRON CX system to calculate and express the glucose concentration.

2. Lipid profiles including:

Total serum Cholesterol was measured using an automated clinical chemistry analyzer (CE, Stanbio Cholesterol LiquiColor® Procedure No. 1010). High Density Lipid Cholesterol HDL-C was measured using Stanbio HDL Precipitating Reagent, Cat. No. 0599. Low Density Lipoprotein Cholesterol: was calculated according to the Friedewald formula: LDL=TC-HDL-TG/5 mg/dl. Triglyceride was measured using StanbioLiquiColor® Triglycerides Procedure No. 2100 Precipitating Reagent, For the Quantitative Enzymatic- Colorimetric Determination of Triglycerides in Serum.

3. HbA1C:

Random blood samples were withdrawal from the patients. We used a standard HbA1c rapid test kit (CE, StanbioGlycohemoglobin Procedure No. 0350, Stanbio Laboratory, and Boerne, Texas).

Assessment of depression:

All participants had a Beck Depression Inventory (BDI) evaluation, The Beck Depression Inventory is a21-question multiple-choice self-report inventory. It is one of the most widely used instruments for measuring depression severity. A value of 0 to 3 is assigned for each answer and the

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

depression severity is determined by the total score, higher scores indicate more severe depressive symptoms. BDI scores of 0–9, 10–18, 19–29 and 30–63 are considered as minimal, mild, moderate and severe depression, respectively (**10)**.

Assessment of Cognitive Impairment:

All participants had Montreal cognitive assessment MOCA test is a 30 points test widely used screening assessment for detecting cognitive impairment. It was validated in the setting of mild cognitive impairment (**11).**

Montreal Cognitive Assessment:

The final version of the MoCA (available at www.mocatest. org) is a one-page 30-point test administered in 10 minutes. Details on the specific MoCA items are as follows. The short-term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately 5 minutes. Visuospatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point). Multiple aspects of executive functions are assessed using an alternation task adapted from the Trail Making B task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points). Attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each). Language is assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points), and the aforementioned fluency task. Finally, orientation to time and place is evaluated (6 points) **(12)**.

Statistical analysis

Data analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance;.Difference and association of qualitative variable by Chi square test (X^2) . Differences between quantitative independent groups by t test, multiple by ANOVA. P value was set at <0.05 for significant results &<0.001 for high significant result.

RESULTS

The present study showed age was distributed as 51.60±14.28, 42.26±12.21 and 51.93±9.89 respectively and Group B was significantly younger than other two groups with no significant difference between them **(Figure 1)**. Group A was significantly lower regard Weight / Kg, BMI and Waist circumference CM than group B&C with no significant difference between them **(Table 1).**

Regarding clinical characters distribution among studied groups, there was no significant different except for Physical activity was significantly associated with Group A & B and hyperlipidemia associated with Group A& C **(Table 2).** Concerning Laboratory investigation, group B was significantly lower regard FBS, PPS and HbA1c than group A&C with no significant difference between them **(Table 3)**.

Regarding Beck Depression Inventory, group A was significantly lower and overall depression was significantly associated with group B and Group C as it was 30.0% and 46.7% respectively **(Figure 2)**.

Our results showed that no significant difference founded among groups as regard cognitive impairment, Type 2 Diabetic patients groups (Group A 26.7%-Group C 33.3)% while group B (Obese non Diabetic) showed less prevalence of cognitive (13.3%) **(Table 4)**.

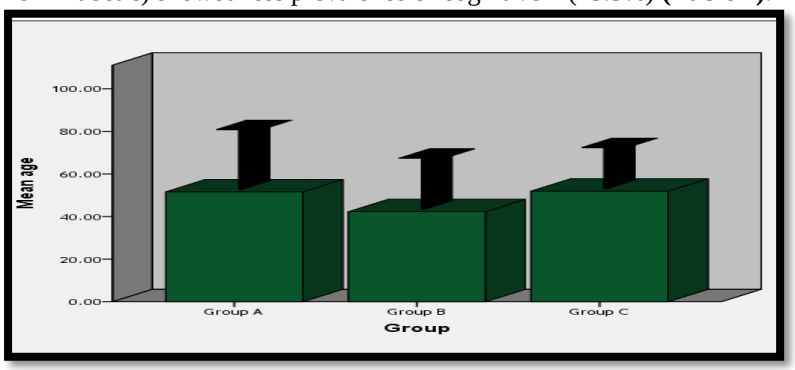

Figure (1): Age distribution between the studied groups.

Table (1): Anthropometric measures distribution among studied groups:

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

	Group A	Group B	Group C	F	P
Height/CM	175.46±8.02	172.73±8.25	172.20±8.07	1.398	0.253
Weight / Kg	74.80±8.673#	110.86±17.73	109.73±16.14	58.148	0.00**
BMI	24.03±1.16#	37.16±4.53	36.92±3.98	134.195	0.00**
Waist circumference CM	84.70±8.97#	122.56±19.18	123.80±21.17	49.557	0.00**

Group significantly lower by LSD, * Group significantly higher by LSD

Table (2): Clinical characters distribution among studied groups:

			Group			X^2	P
			Group A	Group B	Group C		
Family history of diabetes	-VE	N	12	16	12		
		%	40.0%	53.3%	40.0%		
	+VE	N	18	14	18	1.44	0.48
		%	60.0%	46.7%	60.0%		
Physical activity	-VE	N	18	20	28		
		%	60.0%	66.7%	93.3%		
	+VE	N	12	10	2	9.54	0.008*
		%	40.0%	33.3%	6.7%		
Diagnosed hyperlipidemia	NO	N	16	28	12		
		%	53.3%	93.3%	40.0%		
	YES	N	14	2	18	19.66	0.00**
		%	46.7%	6.7%	60.0%		
Total		N	30	30	30		
		%	100.0%	100.0%	100.0%		

Table (3): LAB distribution among studied groups

	Group A	Group B	Group C	F	P
FBS	200.53±69.44	92.33±10.30#	187.06±53.3	40.256	0.00**
PPS	270.60±88.44	113.46±22.13#	239.86±92.54	52.304	0.00**
HbA1c	8.76±2.05	5.24±0.36#	8.19±1.33	52.287	0.00**
Cholesterol	234.73±66.15	217.80±65.26	213.86±33.62	1.133	0.327
TG	204.20±80.12	171.60±58.15	203.33±44.70	2.632	0.078
HDL	55.66±11.07	60.86±10.32	55.53±10.09	2.515	0.087
LDL	114.26±24.97	113.86±19.39	123.13±22.58	1.636	0.201
Total score	25.73±3.98	27.43±5.87	25.86±4.62	1.181	0.235

Group significantly lower by LSD, * Group significantly higher by LSD

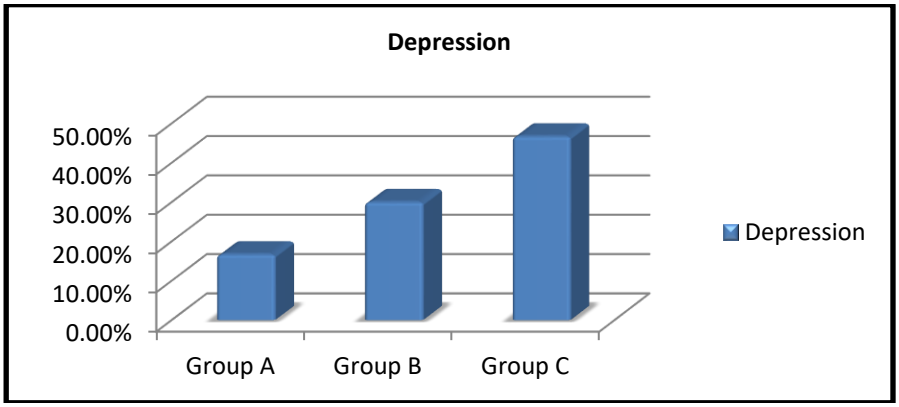

Figure (2): Depression distribution among studied groups

Table (4): Cognitive impairment parameters and overall distribution among studied groups

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

			Group A	Group B	Group C	F/ X^2	P
Executive function			**4.73±0.73**	**5.0±0.0***	**4.86±0.50**	**1.576**	**0.099**
Naming			**2.89±0.40**	**3.0±0.22**	**2.85±0.40**	**1.625**	**0.082**
Attention			**5.33±1.10**	**5.86±0.84**	**5.40±0.92**	**1.773**	**0.069**
Lang			**2.0±0.0**	**2.0±0.0**	**2.0±0.0**	--------	--------
FLUNCY			**0.40±0.21**	**0.66±0.31**	**0.46±0.19**	**2.356**	**0.101**
Abstraction			**0.53±0.28**	**0.85±0.32**	**0.66±0.31**	**2.579**	**0.095**
Delayed Recalling			**3.86±0.89**	**4.03±0.97**	**3.75±1.03**	**1.588**	**0.096**
Orientation			**6.0±0.0**	**6.0±0.0**	**6.0±0.0**	--------	--------
Total score			**25.73±3.98**	**27.43±5.87**	**25.86±4.62**	**1.181**	**0.235**
Cognitive impairment	**-VE**	**N**	**22**	**26**	**20**		
		%	**73.3%**	**86.7%**	**66.7%**		
	+VE	**N**	**8**	**4**	**10**	**3.36**	**0.18**
		%	**26.7%**	**13.3%**	**33.3%**		
Total		**N**	**30**	**30**	**30**		
		%	**100.0%**	**100.0%**	**100.0%**		

DISCUSSION

There is a correlation between type 2 diabetes and mood alterations such as depression and neuropsychiatric disorders; major depressive disorder and mild cognitive impairment. It also has been observed that depression could cause an increase in all-cause mortality risk (approximately 70%); it is also the most common mental disorder and generates a great impact on people in terms of suffering, disability and economic costs, a phenomenon that seems to occur in many parts of the world (**13).**

Obesity has been associated with a higher risk for developing depression **(14).** The distinct mechanisms that link obesity to insulin resistance and diabetes mellitus type 2 are related to an increased production of adipokines and more adipose tissue and they are also associated with arterial hypertension and cardiovascular disease. The adipose tissue of the obese patient becomes resistant to the action of insulin due to the effect of some of these adipokines. This resistance occurs in other tissues; therefore, insulin and glucose levels increase. This increase lead to different adverse events, such as endothelial dysfunction, increase in oxidative stress, impairments in lipoprotein metabolism and increase in blood pressure (**15).**

Diabetes has been shown to be linked to cognitive impairments, especially in the areas of language and memory **(16).** Epidemiological studies have revealed that the risk of incident mild cognitive impairment (up to 60%) and dementia (50–100%) is higher in people with T2DM than in people without diabetes **(17).**

Our study was carried out on 90 adults Divided into Three Groups, 30 patients with type 2 Diabetes Mellitus with normal BMI, 30 obese individuals without DM and 30 obese type 2 Diabetic patients. The aim of this study was to highlighting the relationship between Type 2 Diabetes and Obesity with Depression and Cognitive Impairment.

In our study, age was distributed as 51.60±14.28, 42.26±12.21 and 51.93±9.89 respectively and Group B was significantly younger than other two groups with no significant difference between them

Our results were supported by study of **Habtewold et al.,(18)** as they reported the mean ± SD age at diagnosis and current age of the subjects were 43.9 ± 10.9 and 55.9 ± 10.9 years, respectively.

The present study showed that Group A was significantly lower regard Weight / Kg, BMI and Waist circumference CM than group B&C with no significant difference between them. These results were supported by **Hannon et al., (19)** reported that there were no significant differences in age ($p = 0.66$), sex ($p = 0.75$), BMI ($p = 0.95$), or waist circumference ($p = 0.83$). In the study of **Habtewoldet al., (18)** stated half of the respondents ($n = 132$) had a BMI ≤ 24.9 kg/m2 (mean ± SD, 25.4 ± 3.7).

In the present study, physical activity was significantly associated with Group A & B and hyperlipidemia associated with Group A& C.Group B was significantly lower regard FBS, PPS and HbA1c than group A&C with no significant difference between them. These results are agree with **Knowler et al., (20)** demonstrated that a healthy diet and physical activity can delay or prevent the progression of diabetes and its complications

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

Regarding the laboratory reported fasting blood glucose level, 12.9 % (n = 34) had ≤ 100 mg/dl, 19.7 % (n = 52) 101–126 mg/dl, and 67.4 % (n = 178) had ≥ 127 mg/dl. **Salinero-Fort et al., (21)** revealed no significant differences were observed between patients with depression and psychologically healthy subjects in the level of HbA1c and triglycerides values. They found an inverse association between low physical activity and social support and depression. While this association does not necessarily imply a causal relationship, it might encourage the implementation of physical activity programs and the creation of support groups focused on psychological well-being and detection of depressive symptoms. Some of these suggestions have proven to be effective and feasible in older populations (**22).**

According to **Golden et al., (23)** depressive group had higher fasting insulin, BMI, systolic blood pressure, and estimated total caloric intake but lower physical activity scores (all P values <0.0001). Surprisingly, they also had higher HDL cholesterol (P < 0.0001). There was no difference in waist-to-hip ratio by quartile of depressive symptoms. In our study, no significant difference founded among groups as regard cognitive impairment, Type 2 Diabetic patients groups (Group A 26.7%-Group C 33.3)% while group B (Obese non Diabetic) showed less prevalence of cognitive (13.3).

Different prospective studies have analyzed the association between the presence of type 2 diabetes and the risk of cognitive dysfunction. In older adults (42–89 years), results showed that women with type 2 diabetes had an increased risk of major cognitive decline in verbal fluency after 4 years when compared with non-diabetic women (**24)**. Similarly, other studies revealed the duration of type 2 diabetes point towards an association between the duration of this metabolic disease and a poorer performance in verbal memory and concept formation as well as in general cognition. A longer duration of type 2 diabetes together with an earlier onset, has also been reported to increase the risk of mild cognitive impairment development (**25).**

Our results were supported by a study of **Elshamy et al., (26**) who revealed mild cognitive impairment was confirmed in 22% of diabetic patients and in 9% of control group (p < 0.05) with total MoCA score lower in diabetic group than control one (p < 0.01).

The present study showed that Group A was significantly lower regard Beck Depression Inventory (20%) and overall depression was significantly associated with group B and Group C as it was 30.0% and 46.7% respectively. These results are supported by **Svenningsson et al., (27)** suggested an association between depression and obesity in patients with diabetes mellitus type 2 in both genders; this study reported that at least one in five men and one in three women showed depression in diabetic type 2 patients with obesity.

Cols-Sagarra et al., (28) concluded that the prevalence of depression was high in patients with type 2 diabetes in approximately 40% of patient's depression was undiagnosed. However, the complications related to diabetes and antidiabetic therapy were not associated with the presence of depression.

In the study of **Salinero-Fort et al., (21)** depression is very prevalent among patients with type 2 diabetes and is associated with several key diabetes-related outcomes. Their results suggest that previous mental status, self-reported health status, gender and several diabetes-related complications are associated with differences in the degree of depression. These findings should alert practitioners to the importance of detecting depression in patients with type 2 diabetes.

CONCLUSION

Type 2 Diabetes mellitus associated with high prevalence of Depression and Cognitive Impairment. The results of this study confirm the basis for a better understanding of the association between Cognitive Impairment and depression in patients with diabetes mellitus type 2 and obesity and will allow development of prediction tools and better interventions.

No conflict of interest.

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