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ROLE OF CERTAIN GROWTH FACTORS IN INSULIN RESISTANCE IN A SAMPLE OF IRAQI OBESE PATIENTS WITH TYPE 2 DIABETES MELLITUS ISRAA MUHAMMAD MUBARAK ALDOURI, JABBAR HAMEED YENZEEL

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ABSTRACT

Background: Obesity and type 2 diabetes mellitus (T2DM) are closely interconnected metabolic disorders, with insulin resistance representing a key underlying mechanism. Growth factors such as fibroblast growth factor-21 (FGF21) and transforming growth factor-beta (TGF-β) have been increasingly implicated in metabolic dysregulation; however, their roles in obese Iraqi patients remain insufficiently explored.
Methods: This cross-sectional study included 100 participants divided into three groups: obese patients with T2DM (n=35), obese non-diabetic individuals (n=35), and healthy controls (n=30). Clinical and biochemical parameters, including body mass index (BMI), fasting blood glucose (FBG), and glycated hemoglobin (HbA1c), were measured. Serum levels of FGF21 and TGF-β were determined using enzyme-linked immunosorbent assay (ELISA). Statistical analysis was performed using SPSS, with significance set at $p<0.05$.
Results: Significant increases ($p\leq0.01$) in FBG and HbA1c were observed in the obese with T2DM group compared to other groups. Serum FGF21 and TGF-β levels were significantly elevated in obese patients with T2DM (795.92±126.22 pg/ml and 2360.25±204.51 pg/ml, respectively) compared to controls. No significant differences were observed between obese non-diabetic and control groups. These findings indicate progressive metabolic deterioration associated with insulin resistance.
Conclusion: Elevated FGF21 and TGF-β levels are strongly associated with obesity complicated by T2DM and may reflect underlying metabolic stress, inflammation, and fibrosis. These growth factors could serve as potential biomarkers for insulin resistance and disease progression in obese individuals.

Keywords: Obesity, Type 2 Diabetes Mellitus, Insulin Resistance, BMI, FGF21, TGF-β

1. INTRODUCTION

Obesity is now widely acknowledged as a chronic, relapsing, and multifactorial disease that damages almost all organs with its concurrent metabolic disorders or other related comorbidities like type 2 diabetes, cardio- and cerebrovascular diseases, and cancers. Obesity was caused by a variety of factors, including genetics, biology, healthcare availability, mental status, sociocultural factors, socioeconomics, personal lifestyle, and other environmental inducers. Obesity also affects physical and mental health in several ways that are difficult to resolve through weight loss [1].

Adipose mass accumulation, higher cholesterol, metabolic energy imbalance, insulin sensitivity, lethargy, gallstones, breathing problems, and emotional and social issues are the symptoms. Diabetes mellitus, high blood pressure, coronary heart disease, polycystic ovarian syndrome, and several types of cancer are linked to obesity [2]. Usually, the body mass index (BMI) is used to characterize obesity. However, this metric works better at the population level than it does in characterizing the complexity of obesity as an illness, which calls for a more thorough and systemic evaluation [3].

Recent estimates indicate that by 2030, nearly 14% of men and 20% of women worldwide (more than 1 billion people) will be obese. The percentage of adults who are obese (Class I, II, and III, BMI≥30 kg/m2), severely obese (Class II and III, BMI≥35 kg/m2), and severely obese (Class III, BMI ≥40 kg/m2) will be 18%, 6%, and 2%, respectively [4]. The Middle East and Western Pacific regions are expected to double their childhood obesity population by 2030, with the older age group being mostly responsible for this development. The Western Pacific region has the highest prevalence and numbers of children that suffer from childhood obesity [3]. Siddiqui and Singh (2026)

Obesity is a key driver of metabolic disorders, particularly type 2 diabetes mellitus (T2DM), which is characterized by hyperglycemia due to reduced insulin sensitivity and functional β-cell mass. Obesity plays a role in the development of T2DM by increasing genetic and epigenetic predisposition, insulin signaling, b-cell dysfunction, and microbiome-gut-brain breakdown. In uncommon situations, inborn insulin resistance can become the forerunner of obesity with increased hepatic glucose production and hyperinsulinemia, add on to the weight increase, but this process is not the focus of this research [5].

Obesity and type 2 diabetes mellitus (T2DM) has been a major public health issue worldwide, largely because of the high comorbidity it has with cardiovascular disease, chronic kidney disease and other metabolic complications. Even with the improvement in the pharmacological and surgical procedures, in addition to well-designed lifestyle-modification programs, there is still a significant gap in the long-term clinical treatment of the two conditions. It is noteworthy that intensive lifestyle interventions have proven to be effective in weight loss as well as glycemic regulation over a period of up to two years, which justifies the value of the interventions as a safe and effective initial therapeutic approach in the management of obesity and T2DM [6].

Growth factors are bioactive substances that control cell growth, differentiation and gene expression via definite signal transduction pathways [7]. Their proteins consist of high affinity (>50 amino acids) and peptides (2-50 amino acids) that bind plasma membrane receptors, mainly tyrosine kinase-active ones. Important ones are GM-CSF, VEGF, EGF/EGFR and PDGF. There are also hormones like estrogen and progestogens which are also growth factors. Recent data highlights their critical functions in physiological and pathological mechanisms such as tissue repair, angiogenesis and oncogenesis [8].

Other growth factors, such as EGFR and TGF-β, suppress adipogenesis, whereas others promote it. FGF21 and TGF-β enhance insulin sensitivity as compared to others which enhance insulin resistance. FGF21 increases the growth of the subcutaneous adipose tissue, is positively correlated with insulin sensitivity during obesity, and is a compensatory mechanism in response to systemic IR [9]. TGF-β via the Smad3- pathway inhibits adipogenesis and plays a role in the formation of insulin resistance, making Smad3 a promising therapeutic choice in obesity and T2DM [10].

Therefore, the present study aimed to investigate the role of selected growth factors in insulin resistance among obese Iraqi patients with type 2 diabetes mellitus.

2. MATERIALS AND METHODS

The study was a cross-sectional study, carried out between November 2023 and June 2024, at the National Diabetes Center, Al-Mustansiriya University, Baghdad, Iraq. One hundred participants were recruited and divided into three groups: obese patients with type 2 diabetes mellitus (T2DM), obese patients with no diabetes, and healthy control participants.

All participants were asked to provide written informed consent. The Ethical Committee of the Department of Biology, College of Science, University of Baghdad, approved the study protocol (Reference No. CSCE/1023/0103, approved on October 20, 2023). Clinical diagnosis and anthropometric measures were used to classify participants into study groups.

3. COLLECTION OF SAMPLES AND MEASUREMENT OF BIOMARKER

Approximately 5 mL of venous blood was collected from each participant using standard phlebotomy procedures and transferred into serum-separating gel tubes.

Samples were allowed to clot at room temperature for 15 minutes and were subsequently centrifuged at 3000 rpm for 10 minutes to obtain serum. Serum samples were aliquoted to avoid repeated freeze–thaw cycles and stored at −40°C until analysis, which was performed within two months of collection (Figure 1).

Serum concentrations of fibroblast growth factor-21 (FGF21), transforming growth factor-β (TGF-β) were measured using high-sensitivity sandwich enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions. All samples were thawed only once before analysis to prevent protein degradation.

Commercial ELISA kits were used for quantification of:

- FGF21 (Catalog No. FY-EH1310, China)
- TGF-β (Catalog No. FY-EU1013, China)

Optical density was measured at 450 nm using a microplate reader. According to the manufacturer, the intra-assay and inter-assay coefficients of variation were <10% and <12%, respectively. Hemolyzed samples were excluded, and all serum samples were thawed only once to minimize protein degradation.

Figure 1

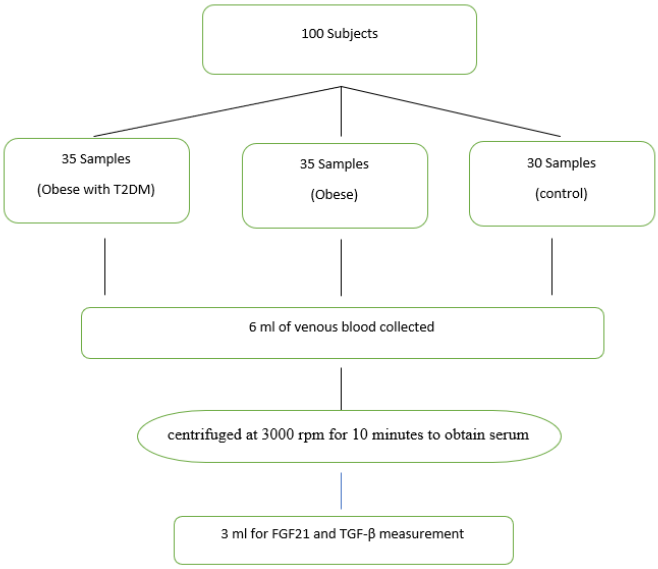

Figure 1 Flow Chart of the Study Workflow

4. STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA). LSD (Least Significant Difference) and Duncan's test were used to significantly compare the means. Chi-Square test was used to significantly compare the percentages. Pearson correlation analysis was applied to examine associations between biomarkers and metabolic variables. A p-value < 0.05 was considered statistically significant.

5. RESULT

Table 1: The present research showed that there was a statistically significant gender distribution across the examined groups. In the Obese with T2DM group (n=35), females constituted the majority at 65.71%, while males represented 34.29%. A similar female predominance was observed in the obese-only group (n=35), where 71.43% were females and 28.57% were males.

Regarding age groups, most individuals under 30 years old were found in the Obese (60%), whereas only 20% of the Obese with T2DM group fell into this category. Interestingly, 40% of the Obese with T2DM patients were over 40 years old, compared to just 8.57% in the Obese group. The age group distribution was highly significant

Table 1

Table 1 Distribution of Patient Groups and Control According to Gender and Age Groups

Factor		Obese+T2DM (No=35)	Obese (No=35)	P-value
Gender	Male	12 (34.29%)	10 (28.57%)	0.022 *
	Female	23 (65.71%)	25 (71.43%)	
Age groups (year)	<30 yr.	7 (20.00%)	21 (60.00%)	0.0019 **
	30-40 yr.	14 (40.00%)	11 (31.43%)	
	>40 yr.	14 (40.00%)	3 (8.57%)	
*** (P≤0.05), ** (P≤0.01)**				

Table 2 showed a significant distribution of obesity classes between the obese with T2DM and the obese groups, indicating a highly significant difference. Among individuals with obese class I (BMI 30–35 kg/m^2), 10 patients (28.57%) were from the obese with T2DM group.

While only 6 (17.14%) were from the obese group. In obese class II (BMI 35–40 kg/m^2), the distribution was nearly equal, with 12 individuals (34.29%) in the obese with T2DM group and 13 (37.14%) in the obese group.

However, obese class III (BMI >40 kg/m^2) showed a higher percentage in the obese group (16 patients, 45.71%) compared to 13 individuals (37.14%) in the obese with T2DM group.

Table 2

Table 2 Distribution of Patient Groups According to BMI (Obese class)

Obese class	BMI (kg/m^2)	Obese+T2DM (No=35)	Obese (No=35)	P-value
Obese class I	30-35	10 (28.57%)	6 (17.14%)	
Obese class II	35-40	12 (34.29%)	13 (37.14%)	0.0022 **
Obese class III	>40	13 (37.14%)	16 (45.71%)	
**** (P≤0.01)**				

In this study, significant differences were observed in age, BMI, fasting blood glucose (FBG), and HbA1c levels among the three groups: obese with T2DM, obese, and control.

Highly significant increase (P≤0.01) was recorded in obese with T2DM group (47.22 ±1.26 years) compared with Obese group (38.51 ±1.19 years) and Control group (37.50 ±1.11 years). No significant difference between the obese group (38.51 ±1.19 years) and control group (37.50 ±1.11 years.

The BMI followed a similar trend, being significantly higher (P≤0.01) in both the obese with T2DM (40.74 ±1.95 kg/m^2) and obese group (39.57 ±0.95 kg/m^2), compared to the control group (22.57 ±0.34 kg/m^2), and there was no significant difference between the obese with T2DM goup (40.74 ±1.95 kg/m^2) and obese group (39.57 ±0.95 kg/m^2).

In FBG, it was a markedly significant increase (P≤0.01) in the obese with T2DM group (237.63 ±13.04 mg/dl), in compared with obese group (102.20 ±3.29 mg/dl) and control group (86.20 ±0.54 mg/dl). No significant difference between the obese group (102.20 ±3.29 mg/dl)) and the control group (86.20 ±0.54 mg/dl)).

Similarly, HbA1c showed highly significant differences (P≤0.01) in the obese with T2DM group (8.59 ±0.24%), followed by the Obese group (5.43 ±0.06%), and in the Controls (4.94 ±0.05%). As shown in Table 3.

Table 3

Table 3 Age, BMI, FBG and HbA1C in Patient Groups and Control

	Means ±SE			
Group	**Age (year)**	**BMI (kg/m²)**	**F.B.G. (mg/dl)**	**HbA1c (%)**
Obese+T2DM	47.22 ±1.26 a	40.74 ±1.95 a	237.63 ±13.04 a	8.59 ±0.24 a
Obese	38.51 ±1.19 b	39.57 ±0.95 a	102.20 ±3.29 b	5.43 ±0.06 b
Control	37.50 ±1.11 b	22.57 ±0.34 b	86.20 ±0.54 b	4.94 ±0.05 c
L.S.D.	3.376 **	** 3.747	22.977 **	0.437 **
P-value	0.0001	0.0001	0.0001	0.0001

Means having with the different letters in same column differed significantly. ** (P≤0.01).

Table 4, FGF21 concentration was highly significant icreased (P≤0.01) in obese with T2DM group (795.92 ±126.22 pg/ml) compared to control group 367.83 ±110.38 pg/ml), and there is no significant differences between obese group (403.78 ±61.42 pg/ml) and control group .

Also, TGF-β levels were highly significant increased (P≤0.01) in obese with T2DM (2360.25 ±204.51 pg/ml) compared to the control group (1526.97 ±160.22 pg/ml), and there is no significant differences between obese groups (1689.86 ±143.64pg/ml) and the control group.

Table 4

Table 4 FGF21 and TGF-β in Patient Groups and Control

	Means ±SE	
Group	**FGF21 (pg/ml)**	**TGF-β (pg/ml)**
Obese+T2DM	795.92 ±126.22 a	2360.25 ±204.51 a
Obese	403.78 ±61.42 b	1689.86 ±143.64 b
Control	367.83 ±110.38 b	1526.97 ±160.22 b
L.S.D.	283.66 **	473.40 **
P-value	0.0069	0.0022

Means having with the different letters in same column differed significantly. ** (P≤0.01).

6. DISCUSSION

This study found statistically significant differences in the gender and age distribution of the considered groups of participants. The women in the obese-only group followed in the current study are in line with the global epidemiological reports that point to the fact that the prevalence of obesity is normally higher in women than in men. To a large extent, this trend can be explained by the sex-specific adipose tissue biology because females have a higher amount of subcutaneous adipose tissue that is metabolically less harmful than visceral fat and can sustain remarkably intact insulin sensitivity at the earlier obesity onset (11,12) It may additionally be related to behaviour about the increased obesity prevalence in women because behavioural factors, such as low levels of physical activity and weight retention during a pregnancy, are associated with obesity (13).

The percentage rate of increase in males may be an indication of progressive insulin resistance of the male sex in the course of long-term obesity, even though females still dominated the obese + T2DM group. Chronic adiposity enhances dysfunction of adipose tissue, inflammation, and insulin desensitisation that eventually leads to the emergence of type 2 diabetes mellitus (14,15).

The progressive nature of the metabolic disease can also be supported by the age distribution that is present in the current study. The younger individuals without diabetes were more likely to have obesity but the people with T2DM were represented by older age groups. It is linked to the aging process and the prolonged exposure to excess adiposity that facilitates the process of obesity to diabetes by increasing insulin resistance, mitochondrial dysfunction, and decreasing 2 -cell efficiency (16,17,18).

The distribution of BMI categories in this research suggests that the people that have obesity-related type 2 diabetes mellitus are more represented with severe obese people. This tendency is consistent with the international

epidemiological evidence that indicates that higher BMI groupings are closely connected with greater metabolic threat (19,20). The growth in adiposity determines the adipose tissue growth by adipocyte hypertrophy that facilitates hypoxia, inflammation, and deficient lipid storage capacity, resulting in the deposition of ectopic fats in the insulin sensitive tissues, including the liver and skeletal muscle (21,22).

The increased representation of diabetic patients in the more extreme classes of obesity confirms the established fact that there is an increasing association between adiposity and insulin resistance. Increased levels of circulating free fatty acids, inflammatory cytokines and adipokine imbalance disregard the insulin signalling pathways and derail glucose metabolism ultimately resulting in β-cell dysfunction and overt diabetes (23,24). Furthermore, chronic low-grade inflammation that additionally promotes the progression of metabolic deterioration characterises severe obesity (17,18).

On the whole, the results support the idea that the intensity of obesity is not merely an excess body mass but also underlying metabolic and inflammatory imbalances that add to the formation of type 2 diabetes mellitus (25).

The age distribution in the current study confirms the established correlation that exists between the ageing process and insulin resistance with the onset of type 2 diabetes mellitus. Older age is linked to gradual decreases in insulin sensitivity, mitochondrial status, and pancreatic β-cell flexibility that predispose to metabolic malfunction with age (26). Therefore, it is possible that obese people are normoglycemic at earlier ages, and, at the same time, the metabolic stress during the ageing process and its accumulated consequences are likely to result in T2DM (27).

The fact that the BMI was also high in both groups of obesity, but the glycaemic profile of the obese+T2DM group proved worse by far, demonstrates the non-homogeneity of obesity phenotypes. Obesity encourages adipose tissue inflammation, liberation of free fatty acids, and blocked insulin signaling, which lead to insulin resistance and metabolic degradation (22,23). The elevating of fasting blood glucose (BG) and higher levels of HbA1C in the obese + T2DM group are therefore indicative of advanced insulin resistance with β-cell dysfunction and persistent hyperglycemia, which aligns with the progression of the insulin resistance that occurs as a result of obesity increasing to overt diabetes (28,29).

Recent studies support the present findings, demonstrating that circulating FGF21 levels are significantly elevated in obesity and further increased in individuals with T2DM. FGF21 is markedly upregulated under metabolic stress conditions, including obesity, insulin resistance, and hepatic dysfunction, and is closely associated with adipose tissue inflammation and cardiometabolic risk (30,31,32). Moreover, its positive correlation with visceral adiposity, dyslipidemia, and insulin resistance suggests that FGF21 functions as a biomarker of metabolic dysfunction rather than metabolic health (33).

The elevation of FGF21 can be interpreted as a compensatory response to metabolic stress that becomes ineffective due to the development of FGF21 resistance. Although FGF21 normally enhances glucose uptake and improves insulin sensitivity, chronic nutrient excess in obesity leads to persistent stimulation of its secretion alongside impaired receptor signaling. Consequently, elevated FGF21 fails to restore metabolic homeostasis, reflecting worsening metabolic dysregulation rather than a protective effect (30,32).

Similarly, the present findings regarding TGF-β are supported by evidence demonstrating its significant elevation in obesity and metabolic disorders. TGF-β plays a central role in metabolic dysfunction through its involvement in fibrosis, inflammation, and tissue remodeling (34,35). Increased TGF-β activity promotes extracellular matrix accumulation, inhibits adipocyte differentiation, and induces adipose tissue fibrosis, leading to reduced tissue expandability and ectopic lipid deposition, which contribute to insulin resistance.

In advanced metabolic disease, including T2DM, further elevation of TGF-β reflects chronic inflammation and progressive tissue damage. TGF-β disrupts insulin signaling pathways, contributes to β-cell dysfunction, and is implicated in the development of diabetic complications such as nephropathy and cardiovascular disease (36).

7. CONCLUSION

This study demonstrates that significant elevations in FGF21 and TGF-β are associated with the progression from obesity to type 2 diabetes mellitus rather than obesity alone. These changes reflect underlying metabolic dysregulation, including insulin resistance, inflammation, and adipose tissue dysfunction. Elevated FGF21 likely represents an ineffective compensatory response due to FGF21 resistance, while increased TGF-β highlights the role of fibrosis in

disease progression. Overall, these growth factors may serve as potential biomarkers for identifying metabolic deterioration and assessing the severity of insulin resistance.

8. STUDY LIMITATIONS

The present study has several limitations. First, the cross-sectional design prevents the establishment of causal relationships between biomarkers and metabolic disorders. Second, the sample size was relatively moderate and limited to a single centre. Third, age differences between study groups may influence biomarker levels. Future studies with larger cohorts and age-matched populations are required to confirm these findings.

ETHICAL CLEARANCE

The study protocol was approved by the Ethical Committee of the Department of Biology, College of Science, University of Baghdad (Reference No. CSCE/1023/0103; approved on October 20, 2023).

CONFLICT OF INTERESTS

None.

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