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Research Article

Role of Insulin-like Growth Factor Binding Protein 7 in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Elevated levels of plasma Insulin-Like Growth Factor Binding Protein 7 (IGFBP7), which is associated with the development and progression of type 2 diabetes mellitus (T2DM). It is increased in patients with T2DM and also increases during diabetes development. The objective of the current study is to find the relationship between IGFBP7 and the occurrence and development of T2DM.
Methods: The current study is a case-control study conducted on 90 Iraqi participants with an average age of 20-70 years during the period between November 2024 and March 2025. The participants were from Imam Hassan Center for Endocrinology and Diabetes in Holy Karbala Governorate, Iraq. The participants were divided into two groups: 60 patients with T2DM and 30 healthy controls. IGFBP7 levels were measured by using an ELISA kit.
Results: IGFBP7 levels were significantly elevated in the patient group with T2DM compared to healthy individuals. It demonstrated an AUC of 0.856 with a probability value of $p < 0.001$ and a sensitivity of 70% and specificity of 70% at a cut-off of 0.86 ng/ml in the current study.
Conclusions: IGFBP7 is a valuable biomarker in diagnosing and developing patients with T2DM, and it is also considered a risk factor for the development of this type of diabetes.

Keywords: IGFBP7; Type 2 diabetes mellitus.

Introduction

Type 2 diabetes mellitus (T2DM) is a category of metabolic disorders marked by hyperglycemia due to impairments in insulin production, insulin action, or both. Two primary kinds of diabetes have been identified: type 1 and type 2. A deficiency or significant reduction in insulin production caused by autoimmune or essential cell death is responsible for T1DM, which constitutes 5-10% of diabetic patients. T2DM is the more common variant, which constitutes about 90% of cases [1]. It typically commences as insulin resistance, a condition wherein cells fail to effectively utilize insulin. As the need for insulin increases, the pancreas progressively diminishes its capacity to synthesize it [2]. Genetic predispositions and lifestyle choices significantly influence the onset of T2DM [3]. The Asian population exhibits a pronounced genetic predisposition to T2DM, manifesting the condition at earlier ages and with a lesser degree of obesity [4]. The prevalence of T2DM has attained pandemic proportions throughout Asia. Despite awareness of the pivotal significance of genetic variables, these have not been included in the clinical assessment of T2DM risk [5]. T1DM is among the most widespread chronic illnesses [6]. Research indicates that the prevalence of T2DM is projected to increase over the next twenty years, particularly among individuals aged 45 to 64 [7-8]. According to the International Diabetes Federation (IDF), almost 463 million individuals globally were afflicted with diabetes in 2020 [9]. In Iraq, two million inhabitants, including 7.43% of the entire population, were projected to be impacted [10]. In 2017, there were 1,411,500 recognized cases of diabetes in Iraq. Globally, 425 million individuals are affected by diabetes, with over 39 million in the Middle East and North Africa (MENA) region. This number is projected to increase to 67 million by 2045. Iraq is one of the 19 countries and territories in the MENA region identified by the IDF [11]. IGFBP7 is a member of a family of structurally related proteins that are strongly linked with the insulin hormone [12-13]. Decreased

insulin secretion and insulin resistance exacerbate T1DM, including reduced oxygen consumption and ATP synthesis in the body [14-16]. IGFBP7 proteins are mostly secreted by the liver and have been investigated as regulators fIGF-1 availability and their potential role in the onset of metabolic diseases [17-18]. IGFBP7 distinguishes itself from other IGFBPs by demonstrating a superior binding affinity for insulin compared to IGF-1 or IGF-2 [19-20]. Additionally, IGFBP7 has been demonstrated to augment insulin action at the insulin receptor in the liver [21] and interacts with the IGF-1 receptor [22]. IGF-1 and the insulin receptor are both members of the receptor tyrosine kinase (RTK) family [23]. The upregulation of the IGFBP7 gene has been associated with β-cell maturation [24]. Insulin resistance correlates with elevated circulating levels of IGFBP7 in non-diabetic males [25], and the IGFBP7 gene in whole blood samples exhibits differential DNA methylation in men recently diagnosed with T1DM [26]. The objective of this study is to investigate the correlation between Insulin-Like Growth Factor Binding Protein 7 (IGFBP7) and the onset and progression of T2DM.

Materials and Methods

Patients

The present study is a case-control investigation conducted from November 2024 to March 2025 at the Imam Hassan Center for Endocrinology and Diabetes in Holly Karbala Governorate, Iraq. The practical component was conducted at the laboratories of the Department of Chemistry and Biochemistry at the College of Medicine at Karbala University in Iraq. The present study involved 60 individuals (30 males and 30 females) aged between 20 and 70 years, all diagnosed with T1DM by a consultant physician based on clinical signs, symptoms, and laboratory testing (FBS, HbA1c). The control group had 30 participants (15 males and 15 females) with an average age ranging from 20 to 70 years. The control group exhibited neither symptoms nor indicators of diabetes mellitus, indicating they were ostensibly healthy. The control group undergoes testing for fasting blood sugar (FBS) and hemoglobin A1C (HbA1c). The tests of blood samples have been conducted at the laboratories of the Department of Chemistry and Biochemistry at the College of Medicine at Karbala University in Iraq. Patients with T2DM were selected based on the diagnosis by the consultant physician according to their clinical signs, symptoms, and laboratory tests (FBS, HbA1c).

To determine whether type 2 diabetes mellitus (T2DM) patients are under control or not, this is done according to the specific criteria for T2DM, which include HbA1c, FBS, and the oral glucose tolerance test (OGTT). If these results are within the specified levels, this indicates that T2DM patients are under control. However, if the results of these tests are outside these limits, this indicates that patients are outside the control of T2DM.

Of the 60 patients in the current study in the diabetic group who were under treatment with anti-glycemic drugs for T2DM, 42 (70.0%) were treated with oral drugs, while the number of patients with treatment by insulin injection was 18 (30.0%). The response of treatment to anti-glycemic drugs in T2DM patients was more than the response of treatment by insulin injection because the glucose levels in T2DM patients with treatment by anti-glycemic drugs were less than the glucose levels in T2DM patients with treatment by insulin injection.

Inclusion Criteria: The patient group was selected with T2DM, and then the control group was selected after showing normal results of FBS and HbA1c tests.

Exclusion Criteria: Excluded patients were those with type 1 diabetes mellitus, chronic liver diseases, chronic renal diseases, chronic heart diseases, chronic joint diseases, cancers, and obesity.

Collection of Blood Samples

Following a minimum fasting period of 12 hours, venous blood was obtained via venipuncture using plastic disposable syringes, collecting up to 5 mL from both control groups and the cohort of patients. Two milliliters were introduced to the EDTA tube for the detection of HbA1c percentage using the latex turbidity technique with the Lifotronic H8 equipment. The remaining 3 mL of blood is allocated to a gel tube, which is subsequently left at room temperature for 30 minutes to commence the clotting process. The material was subsequently centrifuged to isolate the serum at 3,000 ×g for 15 minutes. The sera were split into aliquots for rapid glucose assessment using the enzymatic colorimetric approach with an auto-analyzer system. Serum levels of IGFBP7 are quantified using a competitive immunoassay approach with an ELISA instrument.

Ethical Considerations

The ethical approvals were obtained from the ethical committee team of the College of Medicine at the University of Karbala and the Karbala Health Directorate in Karbala City, Iraq, by the document number 3669 on 21 October 2024.

Statistical examination

The analyses were conducted utilizing IBM SPSS Statistics for Windows, Version 26.0. Descriptive statistics were utilized to summarize the data, with continuous variables presented as mean with standard deviation (mean ± SD) and categorical variables represented as frequencies (n) and percentages. The Kolmogorov-Smirnov test was employed to evaluate data normality. The two-independent-samples t-test was utilized for inferential analysis to compare continuous variables across groups.

The ANOVA test is employed to compare several groups exceeding two in number. Biomarker correlations were assessed utilizing Pearson's correlation coefficient. Relationships between variables were measured using odds ratios (ORs) with 95% confidence intervals (CIs), obtained via unconditional logistic regression. Receiver Operating Characteristic (ROC) curve analysis was performed to ascertain the appropriate threshold for essential diabetics, balancing sensitivity and specificity.

Results

The diabetic group had IGFBP7 at a mean of 1.09±0.33 ng/ml, while the nondiabetic group had a mean of 0.55±0.35 ng/ml with a probability value of $p<0.001$. This was significant, as the diabetic group had higher IGFBP7 levels than the control group (Table 1). The mean of IGFBP7 for males was 0.878±0.472 ng/ml, and for females it was 0.988±0.489 ng/ml, with a probability value of $p=0.325$, which was not significant in the current study, and sex didn't influence IGFBP7 levels (Table 1).

The mean of IGFBP7 for ages from 20 to 40 years was 0.419±0.139 ng/ml, from 41 to 60 years was 0.977±0.288 ng/ml, and for >60 years was 1.376±0.305 ng/ml with a probability value of $p<0.001$, which was significant in the current study. The IGFBP7 levels increase with increasing age, as elucidated in Table 1. The normal weight for IGFBP7 was 0.403 ± 0.202 ng/ml, and the overweight for IGFBP7 was 1.219 ± 0.202 ng/ml with a probability value of $p<0.001$, which was significant in the present study. The IGFBP7 levels increase with an increase in body mass index (BMI) (Table 1). ROC analysis demonstrated strong diagnostic performance for biomarker IGFBP7 that had an AUC of 0.856 with a probability value of $p<0.001$. Sensitivity was 70% and specificity was 70% at a cut-off of 0.86 ng/m in the present study, as indicated in Table 2 and Figure 1.

Table 1: Comparison of IGFBP7 mean values between the study groups.

Biomarker	**Diabetic (n=60) (Mean ± SD)**	**Non-diabetic (n=30) (Mean ± SD)**		**p-value**
IGFBP7 (ng/ml)	(1.09±0.33)	(0.55±0.35)		<0.001
Sex				
Biomarker	**Male (n=30) (Mean ± SD)**	**Female (n=30) (Mean ± SD)**		**P-value**
IGFBP7(ng/ml)	(0.878±0.472)	(0.988±0.489)		0.425
Age				
Biomarker	**20-40 y (n=18) (Mean ±SD)**	**41-60 y (n=23) (Mean ± SD)**	**>60 y (n=19) (Mean± SD)**	**p-value**
IGFBP7 (ng/ml)	(0.419±0.139)	(0.977±0.288)	(1.376±0.305)	<0.001
BMI				
Biomarker	**Normal weight (n=21) (Mean ±SD)**	**Overweight (n=39) (Mean ±SD)**		**p-value**
IGFBP7 (ng/ml)	(0.403±0.202)	(1.219±0.202)		<0.001

IGFBP7: Insulin-like growth factor binding protein 7, SD: standard deviation, NG/ML: nanograms per milliliter, BMI: body mass index, N: Number, Y: year

Table 2: ROC Test of IGFBP7 in diabetic patients group.

Biomarker	**AUC**	**p-value**	**Cut off**	**Sensitivity**	**Specificity**
IGFBP7 (ng/ml)	0.856	<0.001	0.86 ng/ml	0.70	0.70

IGFBP7: Insulin-Like Growth Factor Binding Protein 7, NG/ ML: nano grams per milliliter, ROC: Receiver Operating Characteristics, AUC: Area Under Curve

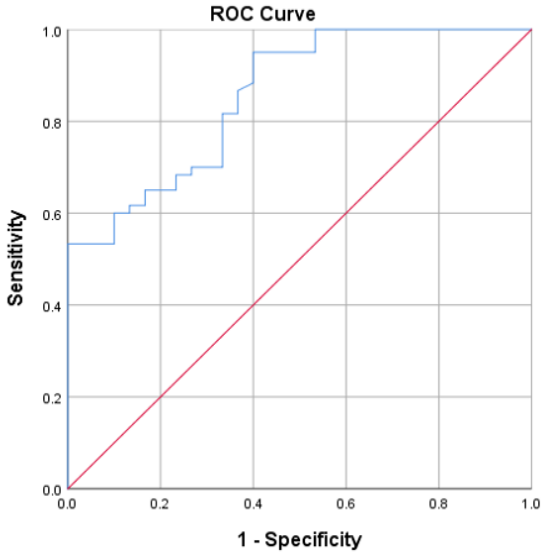

Figure 1: Receiver Operating Characteristics (ROC) curve of (IGFBP7) in the studied groups
ROC: Receiver Operating Characteristic curve, IGFBP7: Insulin-Like Growth Factor Binding Protein 7

Discussion

In the current study, it was observed that the mean of the diabetic group was significantly higher in T2DM patients than in the control group. Previous studies, which showed increasing IGFBP7 levels, have been found in the plasma of T2DM patients and described as statistically significant predictors of T2DM due to the elevated IGFBP7 gene in the islets of the pancreas for the diabetic group more than in the control group, as well as IGFBP7 reduced insulin secretion through impaired p21-activated kinase 1 (PAK1) function, which participates in insulin secretion from pancreas cells. Serum IGFBP7 levels are increased with an increase in insulin resistance for T2DM patients [27].

In the current study, it was observed that there was no statistically significant difference in the mean of IGFBP7 between males and females with T2DM. In a previous study, unlike with the present study, it was found that elevated serum IGFBP7 levels were found in men more than women due to the association of IGFBP7 DNA methylation levels with T2DM in men but not in women [28]. In the present study, it was observed that there were statistically significant differences in the mean of IGFBP7 among T2DM patients. In a previous study, it was observed that IGFBP7 is correlated with age. β cells of the pancreas with advanced age of the patient with T2DM, which leads to the release of IGFBP7 from β cells to the blood. IGFBP7 reduces insulin secretion and increases insulin resistance through impaired p21-activated kinase 1 (PAK1), responsible for insulin secretion and reduced insulin resistance in the body, and this leads to excess blood glucose and IGFBP7 levels [29]. In the current study, we observed that there were statistically significant differences in the mean of IGFBP7 among T2DM patients. In a previous study, it was observed that IGFBP7 is related to body mass index (BMI). β cells of the pancreas with an increase in BMI, which is an increase in insulin resistance, and this leads to the release of IGFBP7 from β cells to the blood [30]. In the present study, it was observed that IGFBP7 showed a strong diagnostic performance with an AUC. Sensitivity was 70% and specificity was 70% at a cut-off of 0.86 ng/ml. In a previous study, it was shown that IGFBP7 had excellent descriptive power with an area under the ROC curve (AUC) [31].

Conclusions

IGFBP7 is a valuable biomarker in diagnosing and developing patients with type 2 diabetes mellitus, and it is also considered a risk factor for the development of T2DM in the present study.

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