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Analysis of the Relationship between HbA1c and Serum IGF-1 Levels in Patients with T2DM

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is characterized by the reduced ability of insulin responses, leading to difficulty in processing blood sugar. It is caused by a combination of two main factors: damaged insulin secretion by pancreatic β cells and the inability of insulin-sensitive tissues to respond to insulin. Blood sugar monitoring in T2DM is done by measuring glycated hemoglobin or Hemoglobin A1c (HbA1c). Insulin Like Growth Factor-1 (IGF-1) is the primary mediator of growth hormone known to play a pivotal biological role in growth and metabolism. This study aims to analyze the relationship between HbA1c levels and serum IGF-1 levels in T2DM patients. The method used was observational analytic with a cross-sectional design. There were 60 T2DM patients involved as research subjects consisting of 26 males and 34 females. HbA1c examination was carried out using the Boronete Affinity Assay, while IGF-1 examination was performed using the Enzyme-Linked Immunosorbent Assay (ELISA) sandwich method. The statistical analysis results showed that the average value and standard deviation of serum IGF-1 levels in controlled T2DM was higher (5740.23±4320.60 pg/mL) than that of uncontrolled T2DM (4843.18±3375.63 pg/mL), showed no significant difference (p=0.462) and no correlation between HbA1c and serum IGF-1 levels in T2DM subjects (r=-0.005 p=0.972). It was concluded that there was no significant relationship between HbA1c levels and serum IGF-1 levels in patients with T2DM.

Keywords: Type 2 diabetes mellitus, serum IGF-1, HbA1c

INTRODUCTION

Diabetes mellitus is a chronic disease with an increase in blood glucose levels due to the pancreas's inability to produce sufficient insulin or the body's ineffective use of insulin, even though it is produced in adequate amounts.[1] According to the American Diabetes Association (ADA), DM is classified into four classes, one of which is type 2 Diabetes Mellitus (T2DM). Type 2 diabetes mellitus is the most significant contributor to all cases of diabetes mellitus around the globe ranging from 90-95% of the occurring cases and has a relatively high prevalence of macrovascular and microvascular diseases, caused by progressive insulin secretion defects triggered by insulin resistance.[1,2]

Measuring glycated hemoglobin (HbA1c) can be used to evaluate blood sugar control, it can evaluate the average blood sugar level over the last 2-3 months in patients with DM. This test can also be a marker and predictor of the development of DM complications.[3] The normal HbA1c level is <5.7%, prediabetes 5.7-6.4%, and diabetes ≥ 6.5%.[1]

Insulin Like Growth Factor-1 (IGF-1) is a hormone with a similar structure and activity to insulin that plays an important role in growth and metabolism; it is synthesized in practically all human body tissues but is primarily produced by liver cells under the control of growth hormone.[4] IGF-1 circulates in the blood; about 97% of IGF-1 is bound to six Insulin Like Growth Factor-Binding proteins (IGFBP-1 to IGFBP-6) and only <1% of the total IGF-1 is in the form of a bioactive free fraction.[5] IGF-1 is also involved in metabolism, including the absorption of glucose absorption and free fatty acid, insulin sensitivity, and glucose uptake by peripheral tissues, which can decrease glucose synthesis in the liver.[6] This hormone also plays a part in cell proliferation and growth.[7]

In several clinical studies analyzing the relationship between IGF-1 and T2DM, lower levels of circulating IGF-1 are involved in the development

of glucose intolerance, complications of T2DM, insulin resistance, and obesity. In a study by Aleidi *et al.*, there was a non-significant negative correlation between serum IGF-1 and HbA1c.[8] Meanwhile, Suda *et al.* also suggested that serum IGF-1 levels decreased significantly in Japanese patients with uncontrolled T2DM.[9]

Changes in IGF-1 levels were observed to be associated with an increased risk of glucose intolerance and DMT2 and were heavily involved in the incidence of the pathogenesis of DMT2 complications, so researchers were very interested in assessing the relationship between HbA1c values and serum IGF-1 levels in patients with T2DM.

METHODS

An observational study with a cross-sectional approach was applied in the current research. The research population was T2DM patients who came to Hasanuddin University Hospital (RSPTN-UH) for a check-up. The sample size was calculated using the formula for non-experimental correlation resulting in 60 samples consisting of 26 males and 34 females. This research was carried out in the Laboratory of Hasanuddin University Medical Research Center (HUM-RC), Hasanuddin University Hospital, Makassar. This research was conducted after obtaining ethical approval from the Health Research Ethics Committee, Faculty of Medicine, Hasanuddin University, RSPTN-UH, with ethical number 136/UN4.6.4.5.31/PP36/2023.

The Boronate Affinity Assay method was used for HbA1c examination and the Human IGF-1 kit from Assay Genie, Irish Factory, for the calculation of IGF-1 levels, by employing the sandwich Enzyme-Linked Immunosorbent Assay (ELISA) method. Data analysis was performed using SPSS software version 22. All the collected data were categorized according to the purpose and type, and the appropriate testing method was then selected. The primary data was processed using the Kolmogorov-Smirnov test to measure the distribution of the existing data. The hypothesis testing showed that the data were not normally distributed, so the Spearman correction test was performed.

RESULTS AND DISCUSSIONS

The study was conducted in April 2023 at Hasanuddin University Hospital, involving 60 T2DM patients. The characteristics of subjects observed in this study were sex, age, duration of illness, HbA1c value, and IGF-1 levels. The 60 individuals included in the study comprised 26 males and 34 females, aged 28 to 84 years old (Table 1).

An independent T-test was conducted to determine the difference in IGF-1 levels between controlled and uncontrolled T2DM with normally distributed data (Table 2). The statistical test obtained a p-value of 0.462 ($p>\alpha$). Thus, it can be concluded that there was no significant difference in IGF-1 levels between the controlled and uncontrolled DM subjects.

Table 1. Characteristics of Research Subjects

Characteristics	Category	DMT2		
		n	%	Mean
Gender	Male	26	43.3	
	Female	34	56.7	
Age	25-39 years	3	5.0	35.33
	40-54 years	16	26.7	48.375
	>55 years	41	68.3	63.122
Duration of illness	1-5 years	26	45.0	
	6-10 years	6	10.0	
	>10 years	27	45.0	
HbA1c levels (%)		60	100	8.94
IGF-1 levels (pg/mL)		60	100	4994.356

Table 2. The difference in IGF-1 levels between the controlled and uncontrolled T2DM

Type 2 DM	n	IGF-1			p
		Range	Median	Mean ± SD	
Controlled (HbA1c <7%)	10	1360.35 - 13514.95	4099.92	5750.23±4320.60	0.462
Uncontrolled (HbA1c =7%)	50	162.79- 11637.166	4330.00	4843.18±3375.63	

Note: Independent T-test (α =0.05)

As seen in Table 3, the results of the Spearman correlation test between HbA1c levels and IGF-1 levels in T2DM patients showed p = 0.972 (p>α). It can be concluded that no significant correlation was found between IGF-1 levels and HbA1c levels in T2DM patients.

Table 3. Correlation test between HbA1c levels and IGF-1 levels

Variable	HbA1c Levels	
IGF-1 Levels	r =	-0.005
	p =	0.972
	n =	60

Note: r = correlation coefficient; p = probability; n = total number (α =0.05)

Figure 1 exhibits that the distribution of data on the scatterplot does not form a linear relationship pattern between the HbA1c and IGF-1, but rather forms a random pattern. This result indicates that there is no correlation between HbA1c and IGF-1.

The current research aims to analyze the relationship between HbA1c values and serum IGF-1 levels in T2DM patients. The characteristics of the research subjects were determined based on their gender and age. This study included 60 patients with T2DM, comprising 26 males and 34 females between the ages of 28 and 84.

As can be seen in Table 2, the independent T-test conducted on 10 controlled T2MD patients (HbA1c <7%) and 50 uncontrolled T2DM patients (HbA1c≥ 7%) obtained a value of p=0.462 (p>0.05). The result indicates that no significant difference was found between IGF-1 levels in controlled and uncontrolled T2DM subjects, even though the controlled T2DM subjects had a higher average and standard deviation of serum IGF-1 levels than the uncontrolled T2DM subjects, with 5740.23±4320.60 pg/mL (HbA1c <7%) and 4843.18±3375.63 pg/mL (HbA1c ≥ 7%). Serum IGF-1 levels were significantly lower in patients with uncontrolled T2DM; as a result of several factors affecting the serum IGF-1, which were not categorized or recorded by the researchers including the nutritional status, liver function, duration of disease, BMI, in addition to uncontrolled glycemia.[9]

The Spearman correlation test revealed a p-value of 0.972 (p>α), indicating no significant correlation between IGF-1 levels and HbA1c levels in patients with T2DM. The result suggested no correlation between the HbA1c and the IGF-1 because the distribution points on the scatterplot form a random/not linear pattern.

A similar result has been shown in previous studies where no correlation was found between HbA1c and serum IGF-1 levels. However, there is a tendency towards a negative association between HbA1c and serum IGF-I levels. Patients with HbA1c ≥ 12% had significantly lower serum IGF-I levels than those with HbA1c < 12%.[9] Similarly, another study found a non-significant correlation between serum IGF-1 levels and HbA1c.[8]

The physiological mechanisms underlying the reduced IGF-I levels in T2DM have not been fully understood. In-vitro, studies show that insulin

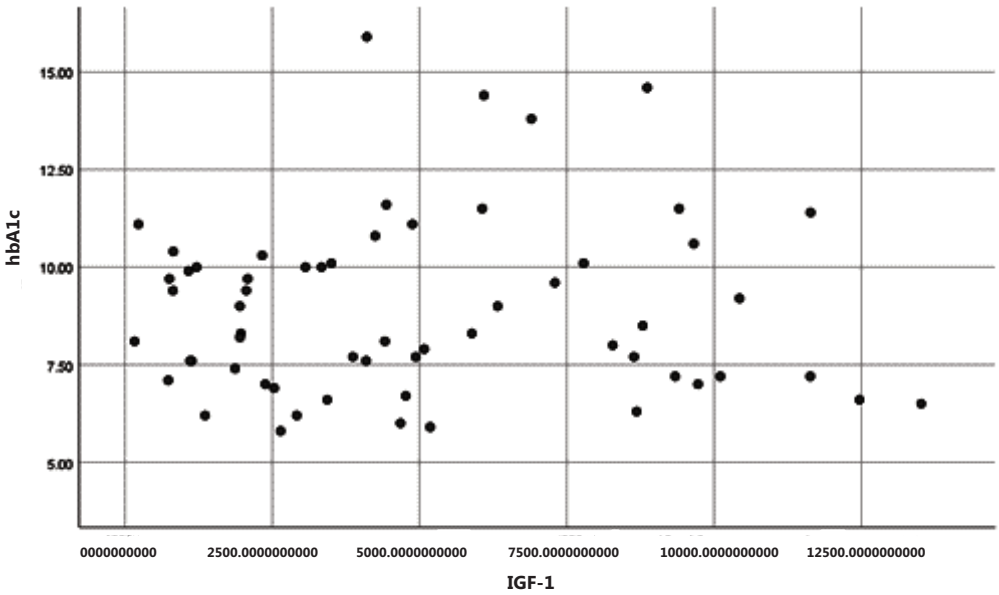

Figure 1. Scatterplot graph of HbA1c and serum IGF-1

modulates the biological action of Growth Hormone (GH) by regulating the biosynthesis of Growth Hormone Receptors (GHRs). The results specify that impaired insulin secretion or insulin resistance may inhibit the expression of GHRs leading to GH resistance and a decrease in IGF-1 synthesis from the liver. There is also a decrease of IGF-1 in insulin-resistant individuals as a result of low secondary GH production in response to high glucose and high levels of circulating Free Fatty Acids (FFA).[8]

There are still various debates regarding serum IGF-1 levels in T2DM patients, low and high IGF-1 levels are associated with insulin resistance.[8,10] Several factors, such as the duration of T2DM could be one of many contributing variables. During pre-diabetes, IGFBP-1 levels are initially lower due to the hyperinsulinemia that occurs in the pre-diabetic phase, which increases in the active form of IGF-1. However, as insulin resistance develops, the liver becomes more resistant to insulin suppression, causing the IGFBP-1 levels to increase accompanied by the decrease of IGF-1 levels. This phenomenon is linked to the decreased sensitivity of body tissues to insulin and increased insulin resistance. In more severe stages of T2DM, IGF-1 levels may decrease further due to liver dysfunction and decreased IGF-1 production. This condition may worsen the symptoms of diabetes and influence the growth and function of body cells.[11]

Research by Caputo *et al.* found that nutritional intake controls IGF-1 levels as well. Protein or calorie intake is regarded as a critical variable. IGF-1 secretion would significantly decrease if calorie intake was cut by 50%. Since proteins have a more significant effect, even a slight decrease in protein levels will alter IGF-1 levels. IGF-1 decreases proportionally to protein intake reductions of 25%. The majority of IGF-1 is synthesized in the liver; proteins and calories play a role in the regulation of liver synthesis. Calories control IGF-1 production while proteins control stability and translation.[11,12] Insulin level secretion is indirectly influenced by variations in carbohydrate intake. Because insulin also controls IGF-1 production in the liver, decreased carbohydrate consumption until less than 700 kcal/day, even consuming more fat won't be able to bring IGF-1 levels back to normal.[13]

Other studies also reported that changes in IGF-1 levels are influenced by age and Body Mass Index (BMI). Hawkes and Grimberg found that the highest average of IGF-1 levels was observed in subjects with BMI between 22.5-25 kg/m^2 in male and 27.5-30 kg/m^2 in female.[14] Furthermore, serum IGF-1 levels also decline with age.[15]

Several limitations were identified based on the experience gained during the completion of this research. The research design utilized cross-sectional data that was recorded only at a single point in time, meaning that IGF-1 levels may have changed during T2DM treatment. The relatively small number of patients and the uneven distribution between controlled and uncontrolled T2DM patients may have influenced the statistical results. Furthermore, influencing variables such as duration of T2DM, nutritional status, BMI, and age were not analyzed.

CONCLUSIONS AND SUGGESTIONS

Based on the results obtained from this study, it can be concluded that there is no significant difference between IGF-1 levels in controlled and uncontrolled T2DM patients. In addition, no significant relationship was found between Hb1Ac values and IGF-1 levels in T2DM patients.

Further research should analyze the difference in IGF-1 levels among T2DM patients with different complications by examining the factors affecting IGF-1 levels. Additionally, researchers should investigate changes in IGF-1 levels in T2DM by comparing them to healthy controls.

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