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IGF-1 Levels in Patients with Type 2 Diabetes Mellitus

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Abstract

Type 2 Diabetes Mellitus (Type 2 DM) is a metabolic disorder group with mechanisms that include hyperglycemia, insulin resistance and hyperinsulinemia. Type 2 DM has a close association with IGF-1, where the active form of the IGF-1 becomes elevated by reason of the fact that hyperinsulinemia inhibits the production of IGF-binding proteins (IGFBP) 1/IGFBP 2. The active form of IGF-1 has the ability to promote cell proliferation and inhibit apoptosis, hence becomes one of the risk factors for cancer cell growth. This was an analytical study conducted in August at the Harapan Bunda Clinic, Medan, Indonesia to determine the difference between the IGF-1 level and blood glucose level in type 2 DM patients in different age groups. Twenty subjects with Type 2 DM participated in this study and were divided based on their age into 35–50 years old or Group 1 (n=10) and 51–65 year old group or Group 2 (n=10). The IGF-1 levels in both groups were compared and analyzed using the T-test dependent method. Results showed that the IGF-1 and blood glucose levels were higher in Group 1 (35-50 years old) when compared to Group 2 and the difference was significant. The change in the IGF-1 level in diabetic patients cannot be determined only by the blood sugar level.

Keywords: Blood glucose level, IGF-1 level, type 2 diabetes mellitus

Kadar IGF-1 pada Pasien dengan Diabetes Melitus Tipe 2

Abstrak

Diabetes Melitus Tipe 2 (DM Tipe 2) merupakan suatu kelompok gangguan metabolik dengan mekanisme penyebab seperti hiperglikemia, resistensi insulin dan hiperinsulinemia. DM tipe 2 memiliki kaitan yang erat dengan IGF-1, bentuk aktif IGF-1 meningkat karena fakta bahwa hiperinsulinemia menghambat produksi protein pengikat IGF (IGFBP) 1/IGFBP 2. Kemampuan yang dimiliki bentuk aktif IGF-1 dalam hal proliferasi sel dan menghambat apoptosis sehingga menjadi salah satu faktor resiko pertumbuhan sel kanker. Penelitian ini dilakukan pada bulan Agustus di Klinik Harapan Bunda Medan untuk menentukan perbedaan kadar IGF-1 dengan kadar glukosa darah pada pasien DM tipe 2 berdasarkan kelompok umur yang berbeda. Penelitian menggunakan 20 sampel pasien DM tipe 2 yang dibagi dalam 2 kelompok, dimana 10 sampel berusia 35–50 tahun (kelompok 1), dan 10 sampel berusia 51–65 tahun (kelompok 2). Desain penelitian yang digunakan adalah penelitian analitik yang membandingkan kadar IGF-1 pada dua kelompok umur yang berbeda. Hasil penelitian dianalisis dengan metode *t-test dependent* dan didapati bahwa kadar IGF-1 pada kelompok umur 35–50 tahun (kelompok 1) lebih tinggi daripada kelompok umur 51–65 tahun (kelompok 2). Simpulan, terdapat perbedaan yang signifikan pada kadar IGF-1 kelompok umur 1 dan 2. Naik-turunnya kadar IGF-1 pada kedua kelompok umur pasien DM tipe 2 tidak hanya dapat ditentukan oleh kadar gula darah.

Kata kunci: Diabetes melitus tipe 2, kadar IGF-1, kadar glukosa darah

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Introduction

Type 2 Diabetes Mellitus (type 2 DM) is one of the major global health problems with 463 million people around the world living with type 2 diabetes in 2019 based on the data from the Diabetes Atlas 2019 (International Diabetes Federation). This number is estimated to continue increasing to 629 million people in 2045. This disease ranks seventh among death-causing diseases in developing countries and Indonesia is the sixth developing country with the highest number of people with type 2 diabetes.[1] The World Health Organization (WHO) has estimated an increase in the number of people with type 2 DM in Indonesia from 8.4 million in 2000 to around 21.3 million in 2030, and will be 2-3 fold higher in 2035.[2]

Type 2 DM is closely related to IGF-1, where the active form of IGF-1 increases when hyperinsulinemia inhibits the production of IGF-binding protein (IGFBP) 1/IGFBP 2. The ability of the active form of IGF-1, along with its receptors, is stronger in cell proliferation and apoptosis inhibition; therefore, the risk of cancer cell growth is. A study from the National Center for Biotechnology Information in 2010 found that low serum IGF-1 is positively related to Diabetes Mellitus in younger subjects and high IGF-1 serum is associated with older subjects.[3,4] This supports Joel Furman's article that stated serum IGF-1 increases with age.[5]

Based on the study from Swapnil and his team, it is suggested that in addition to IGF-1, the IGFBP-1/Insulin Growth Factor Binding Protein-1 also plays an important role in type 2 DM. A high IGFBP-1 level has been shown to cause a decrease in IGF-1 and circulating glucose levels, meaning that IGFBP-1 is a component of IGF-1 regulation.[6] With increasing age, the level of insulin, which contributes to IGFBP-1 and IGF-1 regulation, can be disrupted and lead to unstable effects on IGFBP-1 production.[7]

Age is considered to be linked to the risk for Diabetes Mellitus. One study has shown that the IGF-1 serum level increases with age in children, reaching its peak during puberty and followed by a subsequent decline in adulthood. A similar pattern with age has been found in individuals with diabetes.[8] Patients with Diabetes Mellitus also have decreased functional status and muscle mass loss that increases with age. All of these play a major impact on the ability to manage diabetes independently, making Diabetes Mellitus increasingly out of control. As a result, strategies to improve management in older adults should be selected. The risk of overtreatment of hyperglycemia in older adults also can lead hypoglycemia.[9] This study was designed to evaluate and compare the total serum levels of IGF-I in type 2 diabetic patients aged 35–50 years and 51–65 years.

Methods

This was an analytic cross-sectional study to assess the correlation between the IGF-1 levels of two different age groups of type 2 Diabetes Mellitus patients. This study was conducted in August 2019 at the Harapan Bunda Clinic, Medan, Indonesia, after the approval from the University's Ethic Committee with the issuance of the ethical clearance number 020/KEPK/UNPRI/XI/2020.

The inclusion criteria were controlled type 2 Diabetes Mellitus patient; female or male; aged 35-65 years; and willing to participate in the study. Type 2 diabetes mellitus patients with other comorbidities were excluded.

Subjects were recruited using convenience sampling by including patients presenting to Harapan Bunda Clinic who met the inclusion criteria until the predetermined sample size of 20 was met. Type 2 diabetes mellitus was confirmed through anamnesis and physical examination by medical professionals at Harapan Bunda Clinic. Consent was obtained from these patients through the informed consent process.

Venous blood was sampled at 8 to 9 in the morning after fasting for 10-12 hours. Blood sample was then put in an EDTA vacutainer, centrifuged, and then examined for fasting blood sugar level and IGF-1 level at the Indonesian Laboratory (PATHLAB) Medan. The results of fasting blood sugar level and IGF-1 level examination were then recorded on a data collection sheet and data processing was performed by age group of 35–50 years and 51 to 65 years.

All statistical analyzes were performed using SPSS version 17.0 with a significance level set at p=0.05. To determine the normality of data distribution, the Kolmogorov-Smirnov test was used. When data was proven to be normally distributed, the differences in the mean of two numeric variables were tested using the t-independent test. A correlation test was also applied to assess the relationship between independent and dependent variables. In this study, the independent t-test was used to differentiate the glucose and IGF-1 levels among

Table 1 Subject Characteristics

Age (years)	Gender (n=20)	
	Male	Female
	(n=6)	(n=14)
35–50	5	5
51–65	1	9

two groups while the Pearson correlation test was used to analyze the correlation between IGF-1 and glucose levels.

Results

Twenty type 2 diabetes mellitus patients, predominantly women (n=14), participated in this study. Most participants were 46–50 years old (70%), while the remaining 30% were 40–45 years old (Table 1).

Comparison of fasting blood sugar levels of patients with type 2 diabetes mellitus by age group showed no statistically significant difference (p=0.219), with the average blood sugar level of subjects from the age group of 35–50 years and the older age group (51–65 years) of 177.0±29.70 and 176.1±53.15, respectively (Table 2).

Table 3 presents a statistically significant difference in the IGF-1 level between the two age groups (p=0.047) where the average IGF-1 level of subjects from the age group of 35–50 years (140.60±16.91) was higher than the age group 51–65 years (126.50±42.76).

After the effects of age on blood sugar and IGF-1 levels were revealed among subjects, a correlation analysis between blood sugar and IGF-1 levels was performed. There was no statistically significant correlation between blood sugar level (176.55±41.91) and IGF-1 level (133.55±32.46) in all subjects as reflected in the p-value of 0.209. Although the correlation coefficient is 0.293 which means that there is a very weak correlation between blood sugar level and IGF-1 level, but the correlation is not statistically significant because the p value >0.05.

Table 2 Blood Sugar Level by Age Group

Age (years)	Level of IGF-1 (ng/mL) [Mean ± SD]	p-value
35–50	177.0±29.70	0.219
51–65	176.1±53.15	

Table 3 IGF-1 Level by Age Group

Age (years)	Level of IGF-1 (ng/mL) [Mean ± SD]	p-value
35–50	140.60 ± 16.91	0.047
51–65	126.50 ± 42.76	

Discussion

Women comprised the majority of subjects in this study, which is in line with the finding of Rony in his research at Adam Malik General Hospital Medan showing that the proportion of female patients with type 2 DM was higher than male patients (51% versus 49%).[10] Women are considered to have a greater risk for type 2 diabetes because they have a higher chance for increased BMI (Body Mass Index). The monthly cycle syndrome (premenstrual syndrome) or post-menopause can make body fat easily accumulates, thus increase the risk of women for suffering from type 2 diabetes.[11]

In addition to gender, according Liyanage, age is also seen as one of the reasons for increased incidence of type 2 diabetes because it contributes indirectly to the glucose tolerance. However, direct contribution of age will depend on BMI and physical activities. This is consistent with the theory stating that muscle mass decreases universally as we age. This will result in loss of muscle strength and indirectly contribute to the inability of individuals to carry out daily tasks. Reduced muscle mass and reduced physical activities then contribute to increased body fat and insulin resistance that leads to obesity, which then create changes the levels of plasma glucose, insulin, and glucagon. This is followed by changes in body composition, triggering the development of insulin resistance and diabetes.[12] This is in line with the results of this study, as shown in Table 2, that reveal no significant difference in blood sugar levels between the two age groups.

Insulin like Growth Factor-1 (IGF-1) has a close relationship with type 2 DM. In this study, the IGF-1 component was found to be higher in the younger age group (35–50 years) than in the older age group (51–65 years). This is in contrast with the finding of Garg et al. with results that are inversely proportional to the findings in this study.[3] However, this finding supports the statement of Gong et al.[13] that decreasing IGF-1

levels is associated with osteoporosis in old age. A high IGF-1 level has been associated with the development of lean bones or slender bones which develop during the early age of puberty for up to 52 weeks, affecting general bone growth. This reflects the role of IGF-1 to protect and repair bones, especially during the peak bone mass, and that a decrease in IGF-1 is commonly seen during the period of bone loss .

The increase and decrease in the IGF-1 level cannot be measured through the blood sugar level. According to a study conducted by Clemmons[14], nutrient intake also regulates the IGF-1 level. Calorie or protein intake is an important variable; if the calorie intake is reduced by about 50%, a significant reduction in IGF-1 secretion is seen. The effect of protein is stronger hat even a small reduction in protein will result in changes in the IGF-1 level. For every 25% reduction in protein intake, there is also an equivalent reduction in the IGF-1 level. The majority of IGF-1 is synthesized in the liver. Both protein and calories participate in the regulation of liver synthesis with calories regulate the IGF-1 transcription and proteins primarily regulate stability and translation.[14,15] These result in changes in the IGF-1, especially the active form of IGF-1, which is inversely proportional to IGFBP in type 2 DM. In pre-diabetes, the IGFBP-1 level is initially lower due to the hyperinsulinemia which occurs in the pre-diabetes phase. This condition results in increased active form of IGF-1. However, as insulin resistance develops, the production of IGFBP-1 is inhibited and an increase in the active form of IGF-1 is seen.

To reduce the IGF-1 level, a combination of good nutrition and physical activities is needed. Physical activities can prevent obesity, which may trigger changes in IGF-1 secretion.[16,17] Without a balanced lifestyle, it is possible that the IGF-1 level increases. Elevated levels of IGF-1 are generally associated with cancer risk, including breast, prostate, and colorectal cancers.[18,19,20,21] Several previous studies have further supported the results achieved in this study regarding the lack of direct relationship between blood sugar level and a decrease or increase in IGF-1.

In conclusion, no statistically significant differences were found in blood sugar levels between age groups. Nevertheless, the average IGF-1 level in the younger age group (35–50 years) is higher than that of the older age group (51–65 years) but cannot be determined only by blood sugar level. Therefore, there is no close relationship between type 2 diabetes and IGF-1 level.

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