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Original Article

Correlation between Testosterone Level with HBA1C Level as Glycemic Control Marker among Type 2 Diabetes Mellitus Patient

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Abstract

Background : Type 2 Diabetes Mellitus could cause various complications due to formation of advanced glycation end products (AGEs). The AGEs could destroy many organs into cellular level, one of them is testis, then causing testosterone production deficiency, and hypogonadism. Meanwhile, the AGEs formation in vivo will depend on on mean glucose level in T2DM patient. HbA1C is one of the most common parameter used to asses glycemic control among T2DM patient. This research was conducted to find out the correlation between serum total testosterone with HbA1C level among T2DM patient
Methods : Research subject was collected from Outpatient Polyclinic of Internal Medicine Departement Hasan Sadikin Hospital. HbA1C examination was conducted with turbidimetry method, meanwhile total testosterone level was performed with ELISA method. The examination of research parameter was done at Clinical Laboratory Installation of Hasan Sadikin Bandung.
Results : During sample collection periode, 70 patients was collected and fulfilled the inclusion criteria, 18 of 70 subjects has low testosteron level with Mean (SD): 424.48 (204.82) ng/mL. Correlationntesting between the variables showed r = -0.619 , and p-value <0.001, which means strong and significant correlation between total testosterone and HbA1C among T2DM patient.
Conclusion : There was strong and significant correlation between total testosterone with HbA1C level among T2DM patients, further research could be conducted with prospective cohort method or using free testosterone examination.

Keywords : Diabetes Mellitus, Glycemic, HbA1C, Testosterone

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases which stills become a health problem in the world, including Indonesia. Data from the International Diabetes Federation (IDF) in 2021 shows that globally there are 415 million people with DM in the world. Indonesia is ranked 7th with DM sufferers reaching 10 million people. World Health Organization (WHO) predicts an increase in the number of DM patients at Indonesia in 2030 to around 21.3 million people. Based on the 2019 Basic Health Research (Riskesdas) data, proportion of the Indonesian population aged ≥15 years who were diagnosed with diabetes mellitus (DM) was 6.9 percent.[1] Based on the American Diabetes Association (ADA) and Indonesian Endocrinology Association (PERKENI) in 2021, establishment of DM diagnosis can be made based on the classic symptoms of DM, high blood glucose level, and hemoglobin A1c (HbA1c). Patients who were diagnosed with Type 2 Diabetes Mellitus (T2DM) must be managed comprehensively by controlling food intake, regular exercise, and other pharmacological interventions for the therapy. Pharmacological interventions in T2DM includes oral hypoglycemic drugs (OHO), insulin injections, or even combination of both. Regularity and adherence of T2DM patients to therapeutic management is the key to control blood glucose and preventing complications.[2,3]

Various current studies show that complications of T2DM could also cause hormonal disorders, such as testosterone deficiency in adult men with T2DM. Testosterone is the main androgen hormone in males which takes role in the formation of sexual and reproductive characteristics. This hormone also has other biological roles in the body such as increasing muscle mass, strength, and bone matrix, stimulating erythropoiesis, and supporting cognitive function and emotional stability. Testosterone deficiency can cause clinical symptoms called hypogonadism, which symptoms includes impaired sexual function and reproduction.[4] Impaired sexual function in T2DM patients was also associated with other complications of neuropathy and vasculopathy. However, it is now known that testosterone deficiency due to T2DM plays an important role in the pathogenesis of sexual dysfunction (such as erectile dysfunction) and reproduction (infertility). Therefore, testosterone deficiency in T2DM patients can lead to decreased quality of life.[4,5]

Glycated Hemoglobin (HbA1c) examination is currently used to monitor the control of blood glucose levels in the past 2–3 months and also reflects adherence of patients to the therapy. Hemoglobin-A1c (glycated hemoglobin, glycohemoglobin) is a part of hemoglobin formed as a result of a non-enzymatic glycation reaction between the N-terminal valine of the β chain of hemoglobin A (Hb-A) and glucose. This reaction is continuous and irreversible so that HbA1c can be used as a glycemic control parameter. Based on the Indonesian Endocrinologic Association consensus, results of HbA1c examination can be grouped into some categories, that is: good glycemic control (HbA1c <6.5%), moderate (HbA1c 6.5–8%), and poor (HbA1c >8%).[1,6] Regarding glucose homeostasis, testosterone plays a role in maintaining normoglycemia by increasing insulin sensitivity and glucose uptake in target cells, especially skeletal muscle, adipose and liver. Bad glycemic control, indicated by high HbA1c levels, may be related to low testosterone levels in men with T2DM. Testosterone deficiency in men with T2DM is often undiagnosed and left without treatment. This study is aimed determine the correlation between total serum testosterone levels and HbA1C as a marker of glycemic control in T2DM patients.[6,7]

METHODS

Subjects of this research were men who had been diagnosed with T2DM by clinician from Endocrinology Clinic of Internal Medicine RSUP Hasan Sadikin, met the inclusion criteria, and willing to participate in the study by signing consent. Subjects will be excluded if suffering from abnormalities in testicles, receiving steroid hormone replacement therapy or receive long-term steroid therapy. Patients who met the inclusion criteria will be asked for informed consent, interviewed according to the case report form, then obtained 2cc of blood for HbA1C examination and 2cc for total testosterone examination. Blood sampling was carried out at 07.00–10.00 AM in the morning

Examination of HbA1c levels in this study using quantitative turbidimetric inhibition immunoassay (TINIA) method. The material used is whole blood EDTA. HbA1c levels are stable for 3 days at 15-25°C, stable for 7 days at 2–8°C, stable for 6 months at (-15)-(-25)°C. In this study, the examination material would be checked every time there is a sample. Examination of total testosterone levels in this study used a competitive ELISA method with serum examination materials. The stability of the test material is 8 hours at 18–25°C, four days at 2–8°C, and can last for 6 months at -20°C. In this study, the examination material will be stored at -20°C until the required number of samples is obtained, then examined simultaneously.[8,9]

Data collected then being analyzed with Statistical Package for the Social Sciences (SPSS) version 20. Normality test was performed on HbA1c and total testosterone level The amount of subjects in this study was more than 50, so the normality test was conducted using Kolmogorov-Smirnov's test. If the normality test shows that the data is normally distributed (p>0.05), these variables will be presented in the mean and standard deviation, then statistical analysis will use Pearson correlation test. If normality test shows that the

data is not normally distributed (p≤0.05), the variable will be presented in the median and range (minimum to maximum values), then the next analysis using Spearman correlation test. The correlation will be stated in r-value. The r-value will be considered very weak if <0.2, weak if 0.2–0.4, moderate if 0.4–0.6, strong if 0.6–0.8, and very strong if >0.8. The correlation will be considered significant, if the p-value is <0.05.

RESULT AND DISCUSSION

During the research subject collecting period, 70 subjects met the inclusion criteria and willing to sign the informed consent. Overview of the characteristics of the research subjects is presented in Table 1 including age, duration of T2DM , body mass index, type of medication, adherence to controls and therapy, HbA1c levels, and total testosterone levels. The results of the normality test showed that data on total testosterone level were normally distributed so that they were presented in Table 1 in the form of mean and standard deviation, while data on HbA1c levels were not normally distributed so that they were presented in Table 1 in the form of median and range.

Total testosterone level is normally distributed, meanwhile HbA1c level is not normally distributed, so thus the correlation measurement between the variables will be performed with *Spearman's correlation test*. The result of the correlation test between HbA1C and testosteron level in confidence interval 95% will be presented in Table 3.

According to previous table, *Spearman's correlation test* showed that there was negative correlation between HbA1c with total testosterone lebel, with r-value : 0.619 and p-value <0.001. The results showed that there were strong and negative correlation that is statistically significant. The sample count in this research refers to previous research that found that the correlation of testosterone and HbA1c is with r = -0.346. If the result is compared to the previous research, r-value obtained in this research is bigger than previous one, so it means that the correlation of those variables in this research could be considered as clinically significant.

The correlation graphics of research subject in total testosterone and HbA1c level is provided in Figure 1. The gradient and dispersion of the data in this research showed negative correlation pattern, it means that there is negative and reversal correlation between total testosterone and HbA1c level, it means that higher HbA1C is correlated with lower testosteron level, and also vice versa.

Factors in obesity that plays role in causing testosterone deficiency are increased leptin and pro-inflammatory cytokines (adipokines). Leptin is a hormone produced by adipocytes. An increase in leptin and adipokines will inhibit the release of GnRH resulting in a decrease in LH secretion and eventually cause a decrease in testosterone production by Leydig cells.[10,11]

TABLE 1
Characteristic of Research Subjects (n=70)

Variable		n
Age	30–49 years old	14 (20.0)
	50–59 years old	18 (25.7)
	60–69 years old	26 (37.2)
	≥ 70 years old	12 (17.1)
Duration of Disease	≤ 5 years	45 (64.3)
	6–10 years	11 (15.7)
	> 10 years	14 (20.0)
Body weight	Underweight and normal	21 (30.0)
	Overweight and obese	49 (70.0)
Type of medication	Oral Hypoglycemic Agent	43 (61.4)
	Insulin	17 (24.3)
	Both	10 (14.3)
Compliance of Therapy	Good	41 (58.6)
	Bad	29 (41.4)

SD ; Standard deviation

TABLE 2
HbA1C and Testosteron Level among Research Subjects

Variable	n
HbA1C level (%)	Median (ranges) = 7.24 (4.77–13)
Good glycemic control	18 (25.7)
Moderate glycemic control	26 (37.2)
Poor glycemic control	12 (17.1)
Total testosterone level (ng/dL)	Mean (SD) = 424.48 (204.82)
Deficiency	18 (25.7)
Normal	52 (74.3)

TABLE 3
Correlations between HbA1C and Testosterone Level Among Research Subjects

Variables	r_s (CI 95%)	p-value
HbA1C and Testosterone level	-0.619	< 0.001*

rs = Spearman Rank Correlation; CI = confidence interval
* statistically significant (p<0,05)

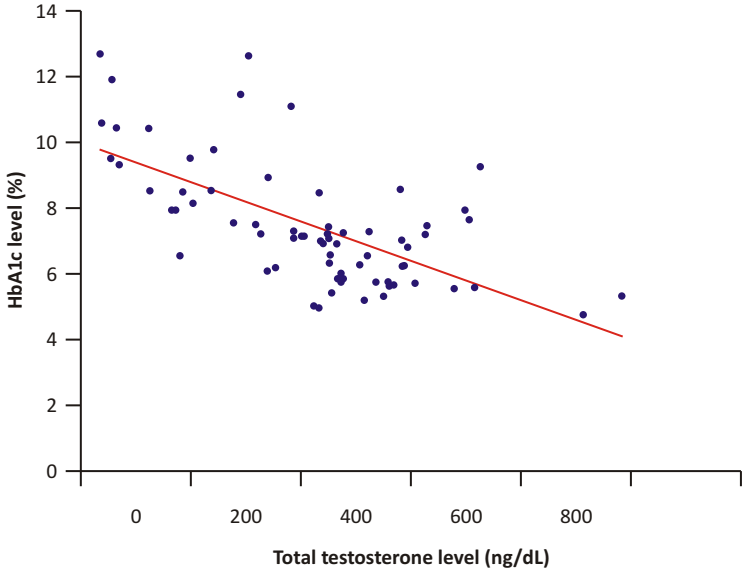

Figure 1. Correlation Graphic between Total Testosterone and HbA1C Level

There were 33.3% (6/18) of testosterone deficient subjects who had testosterone levels <100 ng/dL. All of these subjects were disobedient to control and therapy and also had poor glycemic control. Most of them had already used combination therapy, with a duration of disease varies between 5–13 years. This shows that poor glycemic control reflects non-adherence to control and therapy will make testosterone levels lower. Increasing number of adipose tissue will cause increase in the expression of aromatase which catalyzes the conversion of testosterone to estradiol. Increased estradiol creates a negative feedback on the HPT axis so that testosterone

level will decrease. Fat deposition in the abdomen can also increase testicular temperature that cause testosterone production decreases.[12–14]

Testosterone deficiency has multifactorial causes, such as genetics, age, BMI, and physical activity. Testosterone deficiency is also related to glycemic control, as in this study. Subjects 53, 63 and 66 had low testosterone levels, even though BMI was in the normal category and their age is under 40 years old. These subjects may experience testosterone deficiency due to various other factor. The known risk factors in these subjects are age >50 years and also poor glycemic control, since testosterone decline courd occur after 50 years old in male. The risk factors that were not traced to these subjects were risk of genetics, physical activity, and diet.[14–16]

Insulin receptors are also present on Leydig cells so that insulin binding with insulin receptors on Leydig cells can stimulate testosterone production by Leydig cells. The condition of hyperinsulinemia in insulin resistance can induce the expression of DAX-1, a receptor in the nucleus that will inhibit steroidogenesis in Leydig cells then cause a decrease in testosterone production. Testosterone also has an antioxidant effect that able to prevent pancreatic tissue damage. A study by Phillip (2018), showed that tests on experimental animals given streptozotocin (an alkylating agent that induces damage to the pancreas) showed that in castrated animals (testicles were taken) there was more damage to pancreatic tissue than non-castrated animals. The group that was given testosterone therapy experienced less pancreatic tissue damage compared to group that was not given testosterone therapy.[11] Testosterone plays a role in glucose homeostasis, maintaining normoglycemia by increasing insulin sensitivity and glucose uptake in its target cells, especially in skeletal muscle, adipose and liver. Thus, low testosterone levels play a role in the occurrence of hyperglycemia and were associated with poor glycemic control.[11,16]

Testosterone deficiency in T2DM patients can clinically cause a decrease and impairment in quality of life including some specific symptoms such as impaired sexual and reproductive function, alongside with other non-specific symptoms such as anemia, osteoporosis, decreased stamina, impaired cognitive function, and unstable mood. However, this disorder has not been widely diagnosed in the male population with T2DM since the testosterone level is not routinely screend, then they do not receive therapy. Thus the existence of a negative correlation between HbA1c levels and total testosterone levels in this study could be the basis for further research in Indonesia so screening for testosterone levels can be part of of the therapeutic management of T2DM patients clinically.[11]

CONCLUSION

From this research, it could be concluded that there is strong and statistically significant positive correlation between total testosterone level and HbA1C in Type 2 Diabetes Mellitus patients. Other studies with a larger sample size, which are prospective cohorts, can be conducted to better assess the power of these two variables. Another examination by assesing free testosterone fraction can also be suggested to better assess the testosterone function of the T2DM patients. Another study on focused age group also should be conducted to exclude bias from aging process that could make testosterone lower than normal.

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