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Correlation Analysis of Interleukin-6 on Blood Glucose in Prediabetes and Normal Glycemic Status

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Abstract: Diabetes mellitus is a global health problem whose incidence rate continues to increase yearly. Most people with diabetes mellitus go through the prediabetes phase. Prediabetes is a condition where blood glucose levels are elevated but have not yet reached the criteria for diabetes mellitus. Low-grade chronic inflammation is one of the pathways known to interfere with insulin signalling that ultimately affects blood glucose levels. One of the most studied inflammatory pathways in the pathogenesis of diabetes mellitus is interleukin-6 (IL-6). This study aims to determine whether there were differences in IL-6 levels between groups of prediabetes subjects and normal subjects and to observe the correlation between IL-6 levels and blood glucose. This study is useful in providing additional scientific evidence on the development of diabetes mellitus, especially in blood glucose regulation through inflammatory pathways. The design of this study was analytic observational in 71 subjects with prediabetes or normal glycemic status. Prediabetes status was established based on fasting blood glucose levels and glucose levels 2 hours post oral glucose tolerance test. Subjects with fasting blood glucose levels> 125mg/ dl and who had a fever in the last week were excluded from the study. Interleukin 6 levels were measured based on the principle of enzyme-linked immunoassay. The correlation of interleukin 6 with glucose levels and other variables was analyzed using the spearmen test. The results showed that interleukin 6 levels did not differ between the prediabetes group and the normal group ((5.27 ± 2.55 pg/ml) vs (4.44 ± 2.46) respectively; (p=0.105)). There was no correlation between interleukin 6 level and fasting blood glucose level (r=0.014, p=0.908) and glucose level after the oral glucose tolerance test (r=-0.085, p=0.480). In this study, there was a significant correlation between body mass index with waist circumference (r=0.772, p=0.000) and glucose levels after the oral glucose tolerance test (r=0.240; p<0.001). Recommends the addition of anti-inflammatory cytokines and variable insulin to assess further the effect of the inflammatory process on the glucose metabolism of subjects in future studies.
Keywords: Fasting blood glucose; interleukin 6; oral glucose tolerance test; prediabetes.

INTRODUCTION

The prevalence of diabetes mellitus (DM) continues to increase worldwide, including Indonesia (Badan Penelitian dan Pengembangan Kesehatan Kemenkes RI, 2018; World Health Organization, 2016). The prevalence of diabetes mellitus reached 422 million adults worldwide in 2014 (World Health Organization, 2021).

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This figure is expected to continue to increase until 700 million cases in 2045 (Saeedi et al., 2019). Indonesia is included in the top 10 countries estimated to have the highest number of diabetes mellitus patients in the world (Kementrian Kesehatan Republik Indonesia, 2018). Riskesdas 2018 data shows that more than 1 million Indonesians have diabetes mellitus, which is expected to increase to 21.3 million cases in 2030 (Badan Penelitian dan Pengembangan Kesehatan Kemenkes RI, 2018; Kementrian Kesehatan Republik Indonesia, 2018). Type 2 diabetes mellitus (T2DM) is the most common disease among people worldwide.

This T2DM condition is caused by the body's ineffectiveness in using insulin (insulin resistance), so that increase in blood glucose levels (hyperglycemia) occurs. (World Health Organization, 2016). The condition of increased glucose levels above normal levels but below the criteria for diabetes mellitus is called prediabetes. Prediabetes criteria are characterized by impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) results (Persatuan Diabetes Indonesia & Perkumpulan Endokriologi Indonesia, 2019). The 2018 Riskesdas data stated that the proportion of the population with IFG was 25,274 residents (Badan Penelitian dan Pengembangan Kesehatan Kemenkes RI, 2018). Based on the American Diabetes Association committee, it was stated that 70% of individuals with prediabetes were at high risk of developing T2DM.

The manifestation of T2DM is a chronic impact of impaired insulin signalling in the body, which causes insulin resistance characterized by hyperglycemia. Impaired insulin signalling can be caused by many pathways, one of which is through the mechanism of chronic low-grade inflammation. Cytokine interleukin-6 (IL-6) is a pleutropic cytokine that is not only a pro-inflammatory cytokine but also in the regulation of metabolism, one of which is in the pathogenesis of T2DM (Lehrskov & Christensen, 2019)

Increased IL-6 levels in metabolic pathways are known to be triggered by high-carbohydrate foods (Enga, 2013). Chronic exposure to IL-6 is expected to cause an oxidative stress increase which then causes insulin resistance in T2DM conditions (Agarwal et al., 2017). IL-6 levels were significantly higher in adult T2DM patients (Phosat et al., 2017; Randeria et al., 2019). Studies in the adolescent age group stated that the group of adolescents who have insulin resistance have higher IL-6 levels (De Filippo et al., 2014). Increased levels of IL-6 are also known to correlate with the prognosis of T2DM patients with dyslipidemia (Zhuravlyova et al., 2019). However, in vivo studies showed that the acute effect of increasing IL-6 actually increases glucose uptake and insulin sensitivity in skeletal muscle.

Insulin resistance in T2DM is a chronic effect of hyperinsulinemia and hyperglycemia in the body. Most people with T2DM will go through the prediabetes phase (World Health Organization, 2016). Studies of different levels of IL-6 between prediabetes groups and health groups have been conducted by Hossain et al. (2010) in the Bangladeshi population, and Huang et al. (2022) in the Chinese population still give different results. In another study, a prospective cohort research design found a correlation between IL-6 levels and glucose levels on the prognosis of T2DM development. It is not yet known the report about whether IL-6 correlates with blood glucose levels in prediabetes. This cross-sectional study aims to assess the differences between prediabetes groups and normal groups and determine the correlation between IL-6 levels and blood glucose levels.

MATERIALS AND METHODS

This research was an observational study with a case-control research design. This research received ethical approval from the Health Research Ethics Commission of Tanjung Karang Polytechnic of Health Ministry of Health No.312/KEPK-TJK/XI/2022. The subjects in this study were men and women aged 20-65 years who had no fever for the last week. Only those who signed informed consent were the subjects in this study.

Subjects were asked to fast at night for 8-12 hours, and blood samples were taken the next morning. Oral glucose loading for a 2-hour oral glucose tolerance test (OGTT) examination was carried out according to standard procedures from Perkeni 2021 (Perkumpulan Endokriologi Indonesia, 2021). A total of 71 subjects were grouped into the prediabetes group and the normal group. Individuals with FBG levels of 100-125 mg/dl and or OGTT levels of 140-199 mg/dl were grouped in the prediabetes group, while the normal group were individuals who had FBG levels of 70-99 mg/dl and OGTT levels of 70-139 mg/dl (Perkumpulan Endokriologi Indonesia, 2021). Subjects with FBG >125 mg/dl were excluded from this study. Body mass index (BMI) values were calculated using the formula weight (kg) divided by height squared (m2). Waist circumference (WC) was measured using a non-elastic band and reported in centimetres (cm). Fasting blood glucose and OGTT were examined using whole capillary blood using point-of-care testing. Serum interleukin-6 was examined using Abbkine® (KET6017) based on the ELISA principle at a wavelength of 450 nm and reported in pg/mL.

The age, BMI, WC, FBG, OGTT and IL-6 levels were then analyzed statistically using a testSPSS 26 to observe the differences between groups. Differences in age and IL-6 levels were analyzed using the Mann-Whitney, while the variables of BMI, abdominal circumference and FBG, and OGTT were analyzed using an independent T-test. While the correlation analysis of IL-6 levels on blood glucose levels and other variables was analyzed using the Spearman test.

RESULTS AND DISCUSSION

Table 1. Subjects Characteristics

Variables	Value (n=71)
Sex	
Male	12
Female	59
Age (years)	45.24
BMI	26.62
WC (cm)	
Male	92.08
Female	90.03
FBG (mg/dl)	98.43
OGTT (mg/dl)	127.76
Subject groups	
Prediabetes	36
Normal	35
IL-6 (pg/ml)	4.85

This research was conducted on 71 subjects consisting of 12 men and 59 women with an average age of 45.24 years. The average BMI of the subjects was

26.62. This figure was included in the overweight category for the Indonesian population (Badan Penelitian dan Pengembangan Kesehatan Kemenkes RI, 2018). The subjects' average waist circumference showed that all subjects had central obesity, with an average of 92.08 ± 8.46 cm in male subjects and 90.03 ± 8.44 in female subjects. Central obesity is an absolute criterion for enforcing metabolic syndrome based on criteria published by the International Diabetes Federation, 2006 (Alberti et al., 2006). Obesity is a major risk factor for type 2 diabetes mellitus in children and adolescents (Valaiyapathi et al., 2020). Insulin resistance which is the cause of type 2 diabetes mellitus, is known to be found more in individuals who are obese (Snehalatha et al., 2017). Obesity is significantly correlated with the incidence of gestational diabetes mellitus in pregnant women (Alwash et al., 2021)

This study's average values for FBG and OGTT were 98.42 ± 9.62 mg/dl and 127.76 ± 22.16 mg/dl, respectively. The FBG and OGTT levels were then used to group subjects according to the criteria and examination procedures issued by the Indonesian Diabetes Association and the Indonesian Endocrinology Association. Meanwhile, the average IL-6 level in this study was 4.85 ± 2.52 pg/ml (Table 1).

Table 2. Variable Differences Between Groups

Variabel	Normal (n=35)	Prediabetic (n=36)	p
Age (years)[a]	45 ± 7.92	45 ± 9.43	0.787
BMI[b]	26.51 ± 3.99	26.72 ± 3.48	0.814
WC (cm)[b]	90.96 ± 8.86	89.80 ± 7.94	0.588
FBG (mg/dl)[b]	92 ± 5.34	105 ± 8.10	0.000**
OTGG (mg/dl)[b]	117 ± 12.8	139 ± 23.90	0.000**
Interleukin-6 (pg/ml)[a]	5.27 ± 2.55	4.44 ± 2.46	0.105

[a] Mean difference test was conducted using the Mann whitney test
[b] Mean difference test was conducted using the Independent-T test
*Significance < 0.001

It was found that the average age of the subjects did not differ between groups, namely 45 ± 7.92 years in the normal group and 45 ± 9.43 years in the prediabetic group. The body mass index and WC variables in the two groups were not significantly different. The average BMI in the normal and prediabetic groups were 26.51±3.99 and 26.72±3.48 (p=0.814), respectively, while the mean of WC was 90.96±8.86 cm and 89.80±7.94 cm (p=0.588) respectively.

The levels of FBG and OGTT for the two groups were found to be significantly different (Table 2). There are several criteria for diagnosing prediabetic, including using WHO 2006 criteria, the American Diabetes Association (ADA) 2022 and Perkeni 2021 for the Indonesian population (American Diabetes Association, 2022; Perkumpulan Endokriologi Indonesia, 2021). The definition of prediabetic according to ADA 2022 and Perkeni 2022 is the same, namely, individuals who have an FBG level of 100-125 mg/dl and/or OGTT levels of 140-199 mg/dl. Prediabetic criteria based on WHO 2006 criteria was called intermediate hyperglycemia with a difference in FBG levels of 110-125 mg/dl (World Health Organization, 2006)

In prediabetics, impaired fasting glucose and impaired glucose tolerance indicate abnormalities in carbohydrate metabolism. This condition is characterized by increased blood glucose levels but has not yet reached the criteria for the diagnosis of diabetes mellitus. The level of FBG in this study was found to be significantly correlated with the glucose level of OGTT (r-0.383, p=0.001) (Table 3). Hossain et al. mentioned that individuals with impaired fasting blood glucose and impaired glucose

tolerance are known to have higher insulin levels but lower insulin sensitivity. (Hossain et al., 2010). Evaluation studies of pancreatic B-cell function showed that manifestations of insulin resistance begin to occur in the phase of impaired glucose tolerance (Snehalatha et al., 2017).

Table 3. Correlation Analysis of IL-6 with Blood Glucose and Other Variables

Spearman test		Age	Sex	BMI	WC	FBG	OGTT
IL-6	r	0.047	0.069	0.129	0.124	0.014	-0.085
	p	0.700	0.569	0.283	0.304	0.908	0.480
Age	r		-0.009	0.002	0.098	-0.010	0.080
	p		0.939	0.987	0.415	0.934	0.507
Sex	r			-0.017	-0.128	-0.050	0.039
	p			0.891	0.286	0.681	0.744
BMI	r				.772**	0.071	.240*
	p				0.000	0.556	0.044
WC	r					-0.024	0.132
	p					0.839	0.274
FBG	r						.383**
	p						0.001

BMI=Body Mass Index; WC=Waist Circumference ; FBG= Fasting Blood Glucose; OGTT=Oral Glucose Test Tolerance

*Significance < 0.05

**Significance < 0.001

Research results regarding the correlation of IL-6 in the development of diabetes mellitus are still inconsistent. The results of previous research on Bangladesh's population showed no difference in IL-6 levels between the prediabetes group and the normal group. (Hossain et al., 2010). In the study by Huang et al., namely, IL-6 levels were significantly increased in the prediabetic and diabetes mellitus group compared to the normal group (Huang et al., 2022). IL-6 levels increase with increasing glycemic status in the normal and prediabetes groups that develop into diabetes mellitus (Cho et al., 2020). Retrospective studies showed that individuals with a combination of high levels of C-reactive protein and IL-6 have a 5-fold risk of developing diabetes mellitus. (Lainampetch et al., 2019). The pleotropic nature of IL-6 is known to play a role in developing type 2 diabetes mellitus, especially through inflammation, causing pancreatic beta cell dysfunction and insulin resistance. (Akbari & Hassan-Zadeh, 2018b). Pancreatic B cell dysfunction in prediabetes is mediated by inflammation characterized by increased expression of pro-inflammatory cytokine genes and proteins, including IL-6 (Weaver et al., 2021).

However, this study shows different results. In this study, IL-6 levels were found to be higher in the normal group (5.27 ± 2.55 pg/ml) than in the prediabetic group (4.44 ± 2.46) (Table 2) but not statistically significantly different (p=0.105) (Tabel 3). The results of IL-6 levels were higher in the normal group compared to the prediabetes group but not significantly, as also shown in previous studies. Previous research showed that IL-6 levels in the normal group were higher than in the prediabetes group but increased significantly in the T2DM group (Akour et al., 2017; Butkowski et al., 2016; Lopez et al., 2017). Studies on subjects with metabolic syndrome obtained IL-6 levels that were known to increase significantly in the T2DM group compared to the prediabetes group. This result was followed by an increase in

the level of anti-inflammatory cytokine IL-10 only in the T2DM group. This result is considered an adaptive response due to increased inflammatory signalling.(Lopez et al., 2017). This study did not examine subjects with diabetes mellitus or any anti-inflammation cytokines, so this result cannot be concluded whether it is a strange result or a negative feedback of the immune system in inflammation.

Correlation analysis of IL-6 on fasting blood glucose levels and OGTT glucose levels also found no statistically significant correlation, namely (r=0.014, p=0.908) and (r=-0.085, p=0.480), respectively (Table 3.). Likewise, no correlation was found between IL-6 levels and other subject characteristic variables, including age (r=0.047, p=0.700), gender (r=0.069, p=0.569), BMI (r=0.129, p=0.283), and abdominal circumference (r=0.124, p=0.304) (Table 3). Although it did not show a statistically significant correlation, there was a negative correlation between IL-6 levels and OGTT glucose levels (Table 3). Transcriptomic studies showed that IL-6 mRNA expression negatively correlates with fasting blood glucose levels (Akbari & Hassan-Zadeh, 2018c).

Research results regarding the correlation of IL-6 in the development of diabetes mellitus are still inconsistent. No difference in IL-6 levels was found in the prediabetic group, and the normal group also occurred in the Bangladeshi population (Hossain et al., 2010). Different results were found in the study by Huang et al., namely, IL-6 levels were significantly increased in the prediabetic and diabetes mellitus group compared to the normal group (Huang et al., 2022). IL-6 levels tend to increase with increasing glycemic status in the normal and prediabetes groups that develop into diabetes mellitus (Cho et al., 2020). Retrospective studies showed that individuals with a combination of high levels of C-reactive protein and IL-6 have a 5-fold risk of developing diabetes mellitus. (Lainampetch et al., 2019).

In this study, BMI values were found to have a positive correlation with the subject's OGTT levels (r=0.240; p<0.001) and abdominal circumference values (r=0.772, p=0.000) (Table 3). Body mass index and abdominal circumference, including anthropometric measurements, are known to influence the progression of prediabetes to diabetes mellitus. Prediabetes is a transitional phase in the pathogenesis of diabetes mellitus. Individuals with prediabetes may develop the condition to become diabetes mellitus or return to normoglycemia. The prospective cohort study by Hu et al. found that individuals with prediabetes who returned to a normoglycemic condition were prediabetes individuals with relatively the same average BMI throughout the year of the study. Meanwhile, prediabetes individuals who experienced an increase in BMI have three times the progression to diabetes mellitus. The same was also seen in individuals with prediabetes who experienced increased abdominal circumference (Hu et al., 2020).

Low-grade chronic inflammation in obesity is one of the pathogenesis pathways of diabetes mellitus that has been widely studied. The term metaflamation is a theory that has been developed to describe the link between inflammatory pathways with metabolic pathways (Itoh et al., 2022). Increased IL-6 levels in individuals with insulin resistance correlate with adipose tissue hyperplasia (Almuraikhy et al., 2016). Interleukin-6 is a pro-inflammatory cytokine that not only plays a role in the body's defence mechanism but also plays a role in the regulation of carbohydrate metabolism. Impaired blood glucose homeostasis due to impaired insulin signalling is known to be influenced by the IL-6 signalling pathway in the hypothalamus (Li et al., 2020). A surplus of glucose and lipids is known to be the cause of IL-6 gene expression, and oxidative stress increased through the activation pathway of the Nuclear Factor –κβ (NFκβ) pathway (Nisr et al., 2019). The NFκβ

pathway and IL-6 signal transduction are known to cause impaired insulin signalling. Systemically elevated levels of IL-6 cause activation of the STAT3/SOCS3 pathway in its downstream signalling and interferes with insulin receptors. The activation of SOCS3 also causes the downregulation of GLUT2 and GLUT4, thereby blocking glucose uptake into cells (Long et al., 2020). It is known that the increase in IL-6 levels in the blood is not the result of the secretion of polymorphonuclear cells (Akbari & Hassan-Zadeh, 2018a). It is recommended to add anti-inflammatory cytokines and insulin variables to assess further the effect of the inflammatory process on glucose metabolism in future studies.

Another weakness of this study is that it did not measure the subjects' insulin levels. Insulin is a key hormone in the uptake of glucose into cells. So this study could not see whether IL-6 affects insulin signalling since the prediabetes phase affects the subjects' insulin levels or not.

CONCLUSIONS

The results of this study concluded that there was no statistically significant correlation between IL-6 levels and blood glucose levels of both FBG and 2h-OGTT in subjects with prediabetes and normal glycemic status. recommends the addition of anti-inflammatory cytokines and variable insulin to assess further the effect of the inflammatory process on the glucose metabolism of subjects in future studies.

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CONFLICT OF INTEREST

There is no conflict of interest in this research

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