Jurnal Info Kesehatan
Vol. 21, No. 2, June 2023, pp. 184-191
P-ISSN 0216-504X, E-ISSN 2620-536X
DOI: *10.31965/infokes.Vol21Iss2.933*
Journal homepage:*http://jurnal.poltekeskupang.ac.id/index.php/infokes*

RESEARCH **Open Access**

Immunological Profile of Patients with Controlled and Uncontrolled Type 2 Diabetes Melitus in Mataram City, West Nusa Tenggara

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Received: 7 October 2022 Revised: 31 March 2023 Accepted: 31 March 2023

Abstract

The prevalence of DM disease in West Nusa Tenggara Province is not much different from that in Indonesia. DM cases in NTB are included in the ten most non-communicable illnesses suffered by the community and the incidence continues to increase from year to year. An increase in the levels of pro-inflammatory cytokines in the body is one of the causes of insulin resistance in cells which can further develop into type 2 diabetes. This study involved diabetic patients at the Mataram Community Health Center, who were assigned into 2 groups, namely the controlled diabetes group and the uncontrolled diabetes group and involved a standard group which was a group consisted of healthy people. Each group was examined for Fasting Blood Glucose (FBG) and HbA1c levels. The results of the examination in the standard group, controlled diabetes group and uncontrolled diabetes group obtained the FBG levels of 89.22 mg/dl, 110.0 mg/dl, and 245.80 mg/dl, respectively. Furthermore, the results of the HbA1c test in the standard group, controlled diabetes group and uncontrolled diabetes group were 5.44%, 6.03%, and 10.49%, respectively. The results of the examination of IL-6 levels in the standard group, controlled diabetes group and uncontrolled diabetes were 329.36 pg/ml, 331.52 pg/ml, and 320.33 pg/ml, respectively. The results of the IL-10 test in the standard group, controlled diabetes group and uncontrolled diabetes were 71.80 pg/ml, 116.60 pg/ml, and 128.10 pg/ml, respectively. Based on the results of the study, there was no significant difference in the levels of interleukin 6 and interleukin 10 between respondents with diabetes mellitus and healthy respondents ($p>0.05$). It can be concluded that there were no differences in interleukin 6 and 10 levels between healthy people with patients with controlled and uncontrolled diabetes.

Keywords: Diabetes mellitus, Pro-inflammatory, Interleukin, Glucose, HbA1c, Haemoglobin.

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1. INTRODUCTION

Currently, there are many significant changes in style and pattern of life of all people around the world (Sheng et al., 2019). Lifestyle changes are not for the better, and even in a negative direction, such as frequent consumption of fast food (Junk Food) and lack of activity/exercise (sedentary)(Giri et al., 2020; Sheng et al., 2019). Such changes has led to an increase in the incidence of non-communicable diseases in Indonesia, such as hypertension and diabetes mellitus (DM)(Asril et al., 2020).

In Indonesia, the prevalence of DM sufferers continues to increase (Khan et al., 2020). This can be observed in Basic Health Research data regarding DMin 2007, 2013, and 2018 which showed an increasing trend (Pradono et al., 2021). In 2019, cases of type 2 DM (Non-Insulin Dependent Diabetes Mellitus) became the ten most common diseases in outpatient hajj pilgrims in 2019 with a total of 15,679 patients (Yezli et al., 2021).

The prevalence of DM disease in West Nusa Tenggara Province is not much different from that in Indonesia. DM cases in NTB are included in the ten most non-communicable illnesses suffered by the community and the incidence continues to increase from year to year (Annisa, Puspitasari, & Aini, 2021). In 2018, there were 33,828 DM cases recorded at the CHC, which grew to 41,841 points in 2019. Even in 2019, metabolic diseases, such as DM, both type 1 and type 2, became the cause of death among pregnant women in NTB, as many as 12 cases. In addition, according to data derived from the Indonesian Ministry of Health, in 2019, only 7.79% of patients with DM received standardized health services (Primayanto, 2022)

Type 2 Diabetes Mellitus (type 2 DM) is a metabolic disease caused by the body's failure to process signals from the insulin hormone released by the pancreas (insulin resistance) (Sacerdote et al., 2019). This failure can be due to various factors, including damage or failure of the insulin signaling mechanism in cells (Zamora & Villena, 2019). This failure usually involves Glucose Transporter-4 (GLUT4) and Insulin Receptor Substrate (IRS) in cells (Babu et al., 2020). Such condition may further cause an increase in glucose levels outside the cell since the glucose transport process from outside the cell into the cell cannot take place (Poznyak et al., 2020).

An increase in the levels of pro-inflammatory cytokines in the body is one of the causes of insulin resistance in cells which can further develop into type 2 diabetes (Akash, Rehman, & Liaqat, 2018). An increase in the levels of pro-inflammatory cytokines among patients with type 2 diabetes can be due to obesity (Wang & He, 2018). Various studies found the correlation between an increase in the levels of pro-inflammatory cytokines such as TNF-alpha and IL-6 and obesity (Grosick, Alvarado-Vazquez, Messersmith, & Romero-Sandoval, 2018).

In addition to causing insulin resistance through cell signaling mechanisms, obesity also causes an imbalance between the levels of pro-inflammatory cytokines and anti-inflammatory cytokines (Guo et al., 2020). The increase in the levels of such pro-inflammatory cytokines cause a person to experience a state of low-grade chronic inflammation which can further lead to various complications and the emergence of other metabolic diseases, such as heart disease and hypertension (Villarroya, et al., 2018). In addition, chronic inflammation that occurs continuously and uncontrollably can increase susceptibility of a person to infection (Castro, Macedo-de La Concha, & Pantoja-Meléndez, 2017; Ellulu et al., 2017).

There should be a balance between the levels of pro-inflammatory and anti-inflammatory cytokines to minimize the risk and prevent disease complications related to metabolism. Moreover, mapping of the immunological profile is also required (Bolte et al., 2021). Data on anti-inflammatory and pro-inflammatory cytokine levels are required to get a clearer description of the patient's immunological state. Therefore, researchers are interested in conducting a study on the immunological profile of patients with controlled and uncontrolled type 2 DM patients.

2. RESEARCH METHOD

This was an analytic observational study with a cross-sectional approach. The population in this study were all type 2 DM patients in the Mataram City Community Health Center. Diabetic patients verified by the CHC were initially tested for the levels of fasting blood glucose (FBG) and HbA1c to determine whether they had controlled and uncontrolled diabetes mellitus.

The study samples involved healthy respondents and diabetic patients at the Mataram CHC. There were 50 people as the sample population in this study. Respondents were assigned into three groups: the control group (K) of healthy respondents and two observation groups consisted of type 2 DM patients: the controlled type 2 DM (DT) group and the uncontrolled type 2 DM patients (Figure 2). All respondents were examined for the levels of IL-6 and IL-10. Distribution of the study samples is presented in the chart below.

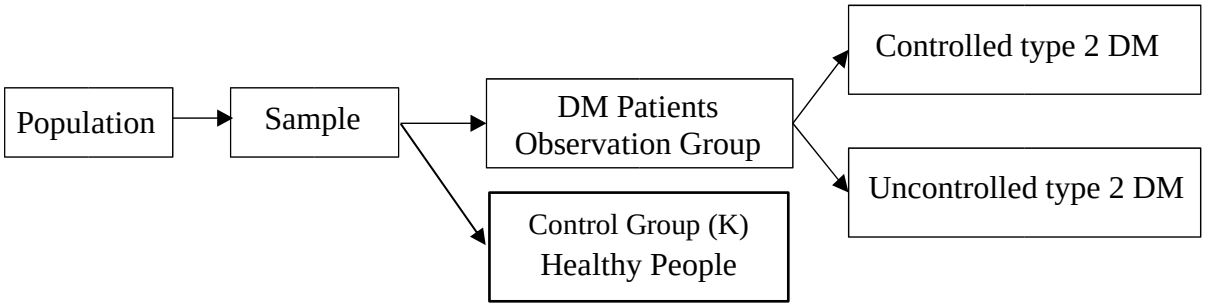

Figure 1. Distribution flow of the study samples. There were 17 respondents with Controlled type 2 DM, 17 respondents with uncontrolled type 2 DM, and 16 healthy respondents.

The inclusion criteria of the study samples involved here were adult male or female patients with age range from 25-60 years, Diabetes mellitus patients who had been diagnosed by a hospital or health care facility, were willing to become respondents, as evidenced by filling out and signing the Informed Consent form, did not have a history of allergies and other immunological diseases such as autoimmune and RA (rheumatoid arthritis), and had no infectious disease either chronic or acute. This study has been approved by the Health Research Ethics Committee, Faculty of Medicine, Al-Azhar Islamic University, through the letter Number 53/EC-03/FK-06/UNIZAR/X/2021.

3. RESULTS AND DISCUSSION

Data regarding laboratory examination in each group of respondents are presented in Table 1. Group assignment for controlled and uncontrolled diabetes was based on the results of FBG and HbA1c levels assessment among respondents with type 2 diabetes mellitus.

Table 1. The Results of Examination for FBG, HbA1c, IL-6, and IL-10 levels.

Variable	Standard	Controlled type 2 DM	Uncontrolled type 2 DM	p-value
FBG (mg/dl)	89.22	110.0	245.80	p <0.05
HbA1c (%)	5.44	6.03	10.49	p <0.05
IL-6 (pg/ml)	329.36	331.52	320.33	p>0.05
IL-10 (pg/ml)	71.80	116.60	128.10	p>0.05

Regarding fasting blood glucose (FBG) levels in each group of respondents, there was a significant difference ($p<0.05$) between the standard respondent group and the Diabetes Mellitus (DM) respondent group. The results of the FBG analysis showed that controlled DM respondents (110.0 mg/dl) and uncontrolled DM respondents (245.80 mg/dl) had different levels of FBG which tended to be higher than average respondents.

Diabetes mellitus is a disease of glucose metabolism disorder characterized by an increase in the levels of glucose in the blood (Xu et al., 2020). The results in this study indicated differences in blood glucose levels between the groups of respondents. Such finding is in line with a study conducted by Amir, Wungouw, and Pangemanan, (2015), which revealed that there were high blood glucose levels among respondents with diabetes mellitus (Amir, Wungouw, & Pangemanan, 2015).

Regarding HbA1c levels, the study results showed a significant difference ($p<0.05$) between the standard respondent group (5.44%) and the uncontrolled DM respondent group (10.49%). Such finding indicated that the HbA1c levels could be a parameter to define the uncontrolled DM group (Sherwani et al., 2016). However, there was no significant difference between the standard respondent group and the controlled diabetes mellitus group. The HbA1c examination is a specific examination to determine high blood glucose levels in the last two to three months (Dağ et al., 2009). This examination can assess the risk of tissue damage caused by high blood glucose levels in the blood (Utomo, Wungouw, & Marunduh, 2015).

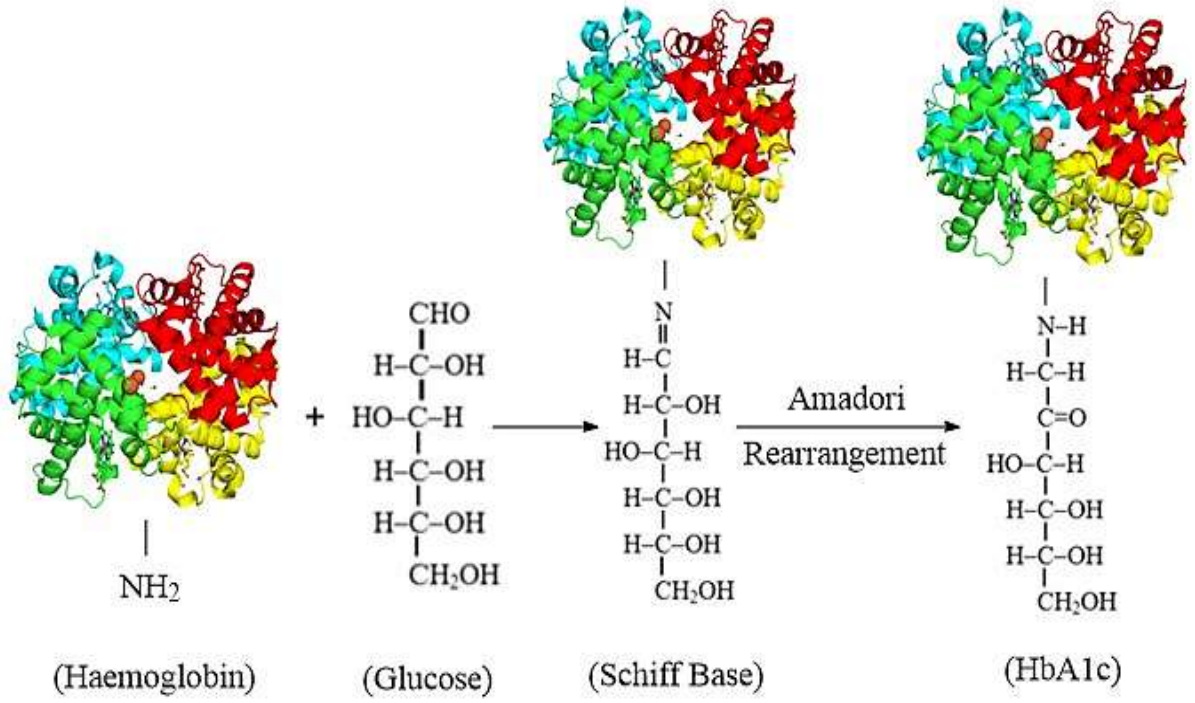

Figure 2. Formation of binding of Hemoglobin Glucose

Glycated haemoglobin (HbA1c) is a monitoring parameter for diabetes which is principally related to the half-life of red blood cells (RBC) (Sherwani et al., 2016). Haemoglobin is a blood component that binds oxygen (Ahmed, Ghatge, & Safo, 2020). The binding mechanism of haemoglobin to glucose can be observed in Figure 2. Haemoglobin will bind glucose non-enzymatically at the N-terminal end of the beta chain of hemoglobin to produce Schiff base aldimine. During the re-arrangement of Amadori, it will become a more stable ketoamine product, namely HbA1c (Muralidharan, Bhat, & Mandal, 2020).

The results of the examination which showed high HbA1c levels in the uncontrolled diabetes respondent group can be due to high blood glucose levels which facilitates the binding to hemoglobin so that it can be used to see a history of high blood glucose levels in the last three months (Silverman et al., 2006). The higher the blood glucose level, the more likely it is to bind to hemoglobin in the blood (Gupta, Jain, & Chauhan, 2017). However, in respondents

with controlled diabetes mellitus, HbA1c levels were not different from average respondents. This could be due to a low-glucose diet to prevent an increase in blood glucose in the blood so that there is no binding of blood glucose to hemoglobin (Paputungan & Sanusi, 2014).

Based on the results of the ANOVA test, there was a no significant difference in the mean level of interleukin 10 between the standard respondent group (71.80 pg/ml) and the controlled DM respondent group (116.60 pg/ml). In addition, there was no significant difference ($p>0.05$) between the standard respondent group when compared to the uncontrolled DM group (128.10 pg/ml).

Interleukin 10 (IL-10) is an interleukin that plays a role in the anti-inflammatory response. IL-10 is produced by immune cells (Treg, Th1, Th2, Th17, Macrophages, DC) in response to inflammation, including IL-6 (Saraiva & O'garra, 2010). IL-10 is a cytokine widely secreted by monocytes, which has a pleiotropic effect on the immune system and inflammation. IL-10 was first recognized for its ability to inhibit activation and effector function of T cells, monocytes, and macrophages (Sabat et al., 2010).

Based on the results of the ANOVA test, there was no significant difference in interleukin 6 (IL-6) levels ($p>0.05$) between average respondents (329.36 pg/ml), controlled DM respondents (331.52 pg/ml), and uncontrolled DM respondents (320.33 pg/ml). IL-6 is produced by adipose cells (adipokines) in response to the polarization of M2 to M1 macrophages among people with obesity (Matsubara et al., 2012; Trayhurn & Wood, 2005). In addition, there is an increase in FFA levels which can activate TLR 4 in adipocytes and produce an inflammatory response (Dasu et al., 2010; Hong et al., 2020).

In this study, there were no significant differences between the standard respondent group with controlled diabetes, and uncontrolled diabetes. Such finding could occur because IL-6 and IL-10 produced from high glucose levels were still able to be suppressed by endogenous and exogenous antioxidants presented in the patient's body so that no increase in IL-6 and IL10 was found (Wang et al., 2020). Diabetes mellitus can cause an increase in the production of free radicals and generate reactive oxygen species (ROS) (Volpe et al., 2018). The increase in free radicals can induce NF-KB to increase Interleukin 6 (Yeo et al., 2018). Reactive oxygen species (ROS) should be reduced so that it cannot generate NF-Kb, and prevent the increase of interleukin 6 (Kida et al., 2021).

In this study, the serum lipid levels were not assessed. Therefore, the relationship between lipid levels and IL-6 could not be revealed. In a survey, it was also found that IL-10 levels were also inversely related to TG and LDL-C levels (Forero et al., 2018; Yuan et al., 2018). Another study also found that in cases of insulin resistance and long-standing incidence of type 2 diabetes, a slight increase in FFA levels was found (Den Hartogh et al., 2020). This was thought to be related to the length of time respondents had suffered from DM, most of which were more than one year.

4. CONCLUSION

High blood glucose can interfere with cell signaling and the immune response of the human body. Still, in our study, there was no significant difference in the interleukin 6 and interleukin 10 levels between respondents with diabetes mellitus and healthy respondents. Elevated blood glucose levels may cause comorbidities that can be harmful to the body. However, the effect of endogenous and exogenous antioxidants consumed by patients with diabetes mellitus can play an important role in preventing the increase in IL-6 and IL-10 levels.

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