The Influence of Type 2 Diabetes Mellitus Comorbidity Factors in COVID-19 Patients on IgM and IgG Antibody Levels of SARS-Cov-2 at M. Yunus Hospital and Harapan Dan Doa Hospital Bengkulu City

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Abstract. The Coronavirus Disease 2019 (COVID-19) outbreak was officially declared a global health emergency by the WHO on January 30, 2020, and poses a high risk to countries with vulnerable health levels. COVID-19 patients may also have comorbid factors for infection with COVID-19. The results of previous studies showed that the most common comorbid factors globally were hypertension (15.8%), cardiovascular and cerebrovascular conditions (11.7%), and diabetes mellitus (DM) (9.4%). These comorbid factors can increase mortality rates in patients infected with COVID-19. This study uses an observational analytical research method in the form of a retrospective study. This study analysed the effect of the comorbid factors of type 2 diabetes mellitus in COVID-19 patients on the level of IgM and IgG anti-SARS-CoV-2 antibodies. The results showed that the comorbid factors of type 2 diabetes mellitus in COVID-19 patients did not affect IgM and IgG antibody levels. Furthermore, the difference between IgM and IgG antibody levels in COVID-19 patients with comorbid type 2 DM and patients without comorbid type 2 DM is insignificant. There is no effect of comorbid type 2 diabetes mellitus in COVID-19 patients on the level of Anti-SARS-CoV-2 IgM and IgG antibodies at M. Yunus Hospital and Harapan and Doa Hospital Bengkulu City in 2020.

Keywords: COVID-19 · Comorbid Factors · Type 2 Diabetes Mellitus · IgG · IgM

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1 Introduction

World Health Organization (WHO) officially declared the Coronavirus Disease 2019 (COVID-19) outbreak as a global health emergency on January 30, 2020. The case of this outbreak was first reported on December 31, 2019, in Wuhan City, Hubei Province, China. The virus that caused this outbreak was then carried out by the Centers for Disease Control and Prevention (CDC) using a throat swab. It was later called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Then WHO introduced the virus that caused the outbreak under the name COVID-19 [1, 2]. The high number of world visitors to Wuhan City in January became one of the biggest causes of the rapid spread of COVID-19.

The government of Indonesia announced the first COVID-19 case on March 2, 2020. Based on data from the Bengkulu Provincial Health Office in Bengkulu Province, as of April 11, 2022, 29,095 cases were recorded [3]. Some clinical symptoms of COVID-19 patients in Bengkulu include fever, cough, chest congestion, fatigue, nausea, anosmia, ageusia, diarrhea, and unconscious [4]. Various efforts have been made to minimise the spread of COVID-19 cases, such as isolating patients who are positive for COVID-19 without symptoms independently, closing access to crowded places, schools, and offices and implementing health protocols [5].

Some cases of COVID-19 can heal independently, but some cases can cause a high enough severity to cause death from infection with SARS-CoV-2. When this virus attacks the patient's body, there will be an immune response to this virus. The body will produce humoral antibodies such as IgG and IgM in response to infection. Progressive IgG and IgM levels increased from day 7 to day 20. IgM usually appears as an early response to infection. IgG, the most abundant antibody in the blood, will provide immunity long after infection [6, 7]. The previous study showed that each patient exhibited varying IgG antibody levels, and patients with mild, moderate, and severe clinical manifestations showed a different trend, respectively [8]. Then, reinfection of SARS-Cov-2 could affect lower IgG levels [9].

According to data from the Indonesian Ministry of Health, the most comorbid factors in COVID-19 cases in Indonesia are hypertension at 50.5%, followed by diabetes mellitus (DM) at 34.5 and heart disease at 19.6% [10]. These comorbid factors can have implications for increasing severity rates in patients infected with COVID-19[11]. Diabetes mellitus (DM) is a chronic, progressive disease considered the most significant global health problem recently [12]. Type 2 diabetes mellitus is a metabolic disorder characterized by increased blood sugar levels caused by decreased insulin secretion by pancreatic beta cells or impaired insulin function. In addition, in type 2 DM, pancreatic beta cells will produce reactive oxygen species (ROS), which causes damage to the pancreatic beta cells [13].

Research on the comorbid factors of type 2 DM and its relationship to IgG and IgM antibody levels in COVID-19 patients has not been widely carried out, so it cannot be used as a reference to assess the effect of comorbid factors on IgG and IgM antibody levels in COVID-19 patients. Based on this background, researchers are very interested in researching the impact of type 2 DM comorbid factors in COVID-19 patients on the levels of IgG and IgM Anti-SARS-CoV-2 antibodies.

2 Methods

2.1 Design of Research

This type of research uses an observational analytical research method in the form of a retrospective case-control study. This study analysed the effect of comorbid factors of type 2 diabetes mellitus in COVID-19 patients on the level of IgM and IgG antibodies against SARS-CoV-2. This research was conducted at the M. Yunus Regional General Hospital and the Harapan and Prayer Hospital in Bengkulu City.

The target population in this study were patients who were confirmed positive for COVID-19 in Bengkulu City in September-October 2020. The affordable population in this study were patients who were confirmed positive for COVID-19 at Harapan and Doa Hospital Bengkulu City and also in M. Yunus Regional General Hospital Bengkulu City in September-October 2020.

There is two groups type of subjects in this study. The first group is subject to the case of DM COVID-19 patients. The inclusion criteria in this study were: patients who were confirmed to have COVID-19, patients over 18 years of age, confirmed COVID-19 patients who received medical treatment for at least 14 days at M.Yunus Hospital Bengkulu City and Bengkulu City Hospital and patients who have comorbid factors of type 2 diabetes mellitus. The second group is subject to the control or non-DM COVID-19 patients. The inclusion criteria are almost the same as the first group, except for one. In the control group, the COVID-19 patients do not have DM comorbid.

2.2 Data Collection

We took secondary data regarding IgG and IgM antibody levels in COVID-19 patients at M. Yunus Hospital and Bengkulu City Hospital in September-October 2020 from previous studies which used Fluorescence Immunoassay (FIA) in the FREND™ system (NanoEntek) [8]. Meanwhile, data on comorbid COVID-19 patients were obtained from the medical records of RSMY and RSHD patients.

2.3 Data Analysis

The analysis technique in this research is bivariate analysis. Bivariate analysis in this study was used to analyse two variables: the independent variable (comorbid factor of type 2 diabetes mellitus) and the dependent variable (level of IgG and IgM antibodies). Bivariate analysis in this study used the ANOVA test. After getting the data, the data will be processed using the Software Statistical Program for Social Science (SPSS).

3 Result

In this study, there were 24 subjects divided into eight patients with comorbid type 2 DM and 16 patients who did not have comorbid type 2 DM. To determine the effect of type 2 DM comorbid factors in COVID-19 patients on the level of Anti-SARS-CoV-2 IgM antibodies, the analysis used is simple linear regression analysis, which is to test

the effect of one independent variable on the dependent variable. X values for comorbid factors and Y values for IgM antibody levels. The basis for decision-making is (1) if the value of sig. < 0.05, then the X variable affects the Y variable; (2) if the value of sig. > 0.05, then the variable X does not affect the variable Y. Table 1 shows the importance of sig. $(0.273) > 0.05$, then the type 2 DM comorbidity variable in COVID-19 patients does not affect the level of Anti-SARS-CoV-2 IgM antibodies.

The effect of type 2 DM comorbid factors in COVID-19 patients on the level of Anti-SARS-CoV-2 IgG antibodies was tested with a similar test. The only difference is changing the Y value for the IgG level. Based on Table 2, it can be seen that the value of sig. $(0.413) > 0.05$, then the type 2 DM comorbidity variable in COVID-19 patients does not affect the level of Anti-SARS-CoV-2 IgG antibodies.

To compare the IgM levels of DM and non-DM patients, the test used was an independent t-test which aims to see the difference in the mean of two unpaired samples. The basis for making decisions for this test are: (1) if the value of sig. (2-tailed) < 0.05, then there is a significant difference in IgM level between DM patients and non-DM patients; (2) if the value of sig. (2-tailed) > 0.05, then there is no significant difference. Based on Table 3, it can be seen that the value of sig. (2-tailed) $0.273 > 0.05$, there is no significant difference between IgM levels in DM and non-DM patients.

The same test was used to compare the IgG levels in DM and non-DM patients. Table 4 shows that the value of sig. (2-tailed) $0.413 > 0.05$, there is no significant difference between IgG levels in patients with comorbid DM and those without comorbid DM.

Table 1. The Effect of Type 2 DM Comorbid Factors on IgM Levels (ANOVA).

Model	***Mean Square***	**F**	**Sig.**
Regression	.282	1.264	.273[b]
Residual	.223		

Table 2. The Effect of Type 2 DM Comorbid Factors on IgG Levels (ANOVA).

Model		*Mean Square*	F	Sig.
	Regression	1621.804	.696	.413[b]
	Residual	2330.822		

Table 3. Comparison of IgM levels of DM patients and non-DM patients.

	Type of group	N	Mean	Sig. (2-tailed)
IgM	Non DM	16	.2463	.273
	DM	8	.4762	

Table 4. Comparison of IgG levels of DM patients and non-DM patients.

	Type of group	N	Mean	Sig. (2-tailed)
IgG	Non DM	16	25.7269	.413
	DM	8	43.1650	

4 Discussion

The results of this study indicate that the comorbid factors of type 2 diabetes mellitus in COVID-19 patients do not affect the level of IgM and IgG antibodies. However, this result is different from previous studies; it was found that serum levels of IgG and IgM in patients with diabetes mellitus were lower than in those without diabetes mellitus. It is due to the condition of hyperglycemia which is characteristic of diabetic patients. Type 2 diabetes mellitus occurs due to insulin resistance in human cells. Therefore, the mechanism of type 2 DM impact in decreasing IgM and IgG levels is due to hyperglycemia inhibiting the production of IgM and IgG in splenocytes [14, 15].

A recent study found that immunity in COVID-19 patients with comorbid diabetes mellitus factors that were controlled and given glucose-lowering drugs could increase and reduce the severity of the COVID-19 virus infection. In addition, recent research found that dipeptidyl peptidase-4 (DPP4) inhibitors have anti-inflammatory effects. Therefore, they can reduce macrophage infiltration and play a significant role in glucose and insulin metabolism. Some DPP-4 drugs commonly used for treating diabetes are sitagliptin, vildagliptin, saxagliptin, and linagliptin. It is why DPP-4 inhibitor drugs will increase immunity in patients who are infected with the COVID-19 virus. In addition, other studies have also found that metformin, a drug that blocks the increase in blood sugar levels, can improve immune function. It is related to the function of metformin which can maintain pancreatic homeostasis so that it can significantly increase insulin sensitivity and signaling, which plays a role in increasing immunity and fighting infection. In addition, metformin can increase cellular and endosomal pH. It also can suppress the endocytic cycle and virion maturation [16].

In other research results, other factors can also increase immunity in patients infected with COVID-19 despite having comorbid factors called oxygen saturation [17]. The results of previous studies showed that low oxygen saturation was a marker of suppression of antibody production and T cell immunity by the virus. In the case of COVID-19 patients, the virus can interfere with the work of the alveoli in the lungs, which function as a place for oxygen and carbon dioxide exchange, so that the oxygen supply will be disrupted. The interrupted oxygen supply will also interfere with the production of red blood cells in the bone marrow, which require oxygen for their formation. It results in immature red blood cells that cannot carry out their function to carry and circulate oxygen throughout the body. In addition, immature red blood cells will become the target of the COVID-19 virus in infected patients because they have ACE2 and TMPRSS2 receptors, the attachment sites for the SARS-CoV-2 virus. They will result in insufficient oxygen supply in the tissues. These immature red blood cells are immunosuppressive [18].

In this study, based on the sample profile that was collected and contained in the patient's medical record data, it was found that the oxygen saturation of patients infected with COVID-19 and having comorbid type 2 diabetes mellitus was still relatively high (>85%). Therefore, it can also be one of the factors that cause the subjects in this study to have pretty good immunity.

It was also found that the level of IgM and IgG antibodies in COVID-19 patients with type 2 DM comorbid factors and those who did not were not significant in a previous study. Based on the results of previous studies, it was found that in patients with type 2 diabetes mellitus, IgG titers will increase from week one to week three, followed by stabilization, and then decrease in week four. IgM levels will increase from week 1 to week two or three and decrease after that [19]. The results of previous studies showed a different trend in IgG levels in the three categories of clinical manifestations [8].

The difference between patients with comorbid type 2 diabetes mellitus and those without comorbid type 2 diabetes mellitus is visible. IgG levels in patients with type 2 DM have a higher quantitative response in the second and third weeks than those without comorbid type 2 DM factors. Otherwise, IgM levels in patients with comorbid type 2 DM factors will decrease earlier than in patients who do not have comorbid factors for type 2 DM. In addition, other factors can affect antibody levels in COVID-19 patients, which are the clinical manifestations that appear in these patients. The clinical manifestations of these patients can be categorized into mild, moderate, and severe [19].

The results of other studies also stated that immunity could be influenced by food intake and balanced nutrition. Based on the results of previous studies, it has been found that macro and micronutrients will work in harmony to maintain the body's resistance to infection. Macronutrients (such as protein and omega 3) can help in the formation of immunoglobulins and reduce inflammation in the incidence of COVID-19 virus infection. In addition, micronutrients (such as vitamin A, amino acids, vitamins B6 and B12, vitamin C, vitamin D, zinc, etc.) can improve the natural immune system as antioxidants and increase body immunity so that patients who experience COVID-19 virus infection can recover faster [20].

One of this study's limitations is that the researchers only used blood samples from patients on the first day of being tested positive for COVID-19. The number of samples used in this study is also minimal. In addition, the research subjects are only in the scope of two hospitals in Bengkulu, so it cannot describe the effect of comorbid factors on IgM and IgG antibody levels in COVID-19 patients in Bengkulu Province in Indonesia.

5 Conclusion

Based on the data analysis and discussion results, it can be concluded that the comorbid factors of type 2 diabetes mellitus in COVID-19 patients have no effect on IgM and IgG antibody levels in patients with a history of type 2 diabetes mellitus. In addition, the comparison of IgM and IgG antibody levels in COVID-19 patients with comorbid type 2 DM factors with those who do not have type 2 DM comorbid factors is not significant.

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