A Systematic Review: Evaluation of Treatment for Diabetes Mellitus with Comorbidities Who Have Been Vaccinated Against COVID-19

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Abstract: Diabetes mellitus is a chronic metabolic condition characterized by persistent hyperglycemia. Diabetes mellitus is a major public health problem with a wide impact because it can cause other comorbidities such as hypertension, heart and blood vessel disease, stroke, kidney failure, blindness, leg amputation, and death. This study aims to determine the treatment evaluation of patients with diabetes mellitus with comorbidities who have been vaccinated with COVID-19. Literature review using research reports from several journal databases, namely Google Scholar, PubMed, Science Direct, and Vaccine. The article search used the PICOS method and the analysis was carried out qualitatively. The results of the stTTudy obtained 23 research reports. The results of the systematic review that have been reviewed are the most widely used drugs as a treatment for diabetes mellitus, namely metformin both single and combined, then the sulfonylurea group. The most widely used treatment for comorbid hypertension is candesartan. The conclusion from the literature review is that the evaluation of diabetes mellitus treatment with comorbidities is by the management guidelines and overall is appropriate, namely the right indication, the right drug, the right dose, the right method of administration, the right time interval and the right duration of administration.

1 INTRODUCTION

Diabetes mellitus is a medical condition in which blood glucose levels rise above normal levels. Sugar levels remain high in the blood, which can be caused by insulin not being produced, insulin that is insufficient for the body's needs, or ineffective. Diabetes mellitus is currently one of the global health threats (Endocrinology Society Indonesian).

WHO predicts that globally there will be a considerable increase in the number of patients with type 2 diabetes mellitus in the coming years. Meanwhile, the prevalence in Indonesia is predicted to be around 21.3 million in 2030. The International Diabetes Federation (IDF) predicts that in 2045 people with diabetes mellitus in Indonesia will reach 16.6 million (IDF, 2019). Based on data from Basic Health Research (Riskesdas, 2018), the prevalence of diabetes mellitus in Indonesia has increased to 8.5% (Ministry of Health of the Republic of Indonesia, 2018).

In general, the goal of diabetes mellitus management is to improve the quality of life of diabetic patients and the ultimate goal of management is to reduce the morbidity and mortality of diabetes mellitus (Endocrinology Society of Indonesia, 2021). Diabetes mellitus is one of the non-communicable diseases and is also called the "silent killer" and "Mother of disease" which is the carrier or parent of other diseases or other comorbidities such as hypertension, heart and blood vessel disease, stroke, kidney failure, blindness, leg amputation until death. (Meryta and Fachdiana, 2023).

Diabetes mellitus is one of the main risk factors for Covid-19 exposure. People with diabetes mellitus are susceptible to infection due to hyperglycemia, impaired immune function, vascular complications, and other comorbidities such as hypertension, dyslipidemia, and cardiovascular disease. The severity and mortality of COVID-19 are significantly higher in patients with diabetes mellitus than non-diabetes mellitus. Due to a decrease in the function of the body's immune system, people with diabetes mellitus are one of the factors that trigger the young Covid-19 during the pandemic. (Jeong et al., 2020).

According to data from the Indonesian Ministry of Health, 70% of the 8,320 patients who died from covid-19 had not received the full vaccine. The COVID-19 vaccine can significantly reduce the severity of the disease course and death. In addition,

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a low immune system can produce strong antibodies after vaccination, so the COVID-19 vaccine is very important for susceptible patients. (Asriati et al., 2023).

Combined efforts between pharmacological and non-pharmacological therapies can be part of the management of diabetes mellitus and its comorbidities. Patterns and conformity with standards, especially oral antidiabetics as the first line of pharmacological therapy for type 2 diabetes mellitus, are very important for proper therapy. (Endocrinology Society Indonesian.

Based on the research of Inayah et.al (2016), the treatment of diabetes mellitus with comorbid hypertension mostly uses metformin and candesartan drugs. Where this is by PERKENI 2021. Administration of hypertension drugs in the calcium channel blocker group can improve cardiovascular performance (Inayah et al., 2016).

Research Jonathan et.al (2019) patients with type 2 diabetes mellitus are mostly given single drug therapy (65.2%), namely metformin. If single therapy has not reached the target (HbA1C), a combination therapy of 2 drugs with different mechanisms is given, if the combination therapy of 2 drugs has not reached the target, it is increased to a combination therapy of 3 drugs with different mechanisms. This is by the management of diabetes mellitus regulated by Perkeni 2021. (Jonathan et al., 2019).

Based on Pratama and Ratnasari's research (2021), the most widely given diabetes mellitus treatment is a combination of two oral antidiabetics, namely metformin and glimepiride. Aims to better control the patient's blood glucose with different mechanisms of action of the drugs. Then additional vitamin drugs such as mecobalamin are given to treat comorbid diabetic neuropathy patients. (Pratama and Ratnasari, 2021).

According to research by Nuraisyah et al. (2022) the use of drugs for patients with diabetes mellitus with stroke complications both combination and single is dominated by the use of parenteral antidiabetic drugs such as novorapid injection, while the most widely used oral antidiabetic drugs such as glimepiride, calcium channel blocker antihypertensive drugs, antiplatelet drugs. (Octariani et al., 2022)..

Based on the background that has been described, the authors consider it is necessary to conduct a systematic review study to discuss and examine various scientific information regarding the evaluation of treatment of patients with diabetes mellitus with comorbidities who have been vaccinated with COVID-19.

2 METHODS

This study is a systematic review, using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) method which is carried out systematically by following the correct stages or research protocols. The procedure of this systematic review consists of several steps, namely 1) compiling Background and Purpose, 2) Research Question, 3) Searching for the literature 4) Selection Criteria 5) Practical Screen 6) Quality Checklist and Procedures 6) Data Extraction Strategy, 7) Data Synthesis Strategy.

This study was conducted in June-August 2023 in Jakarta. The search for research articles relevant to the topic of this study was carried out using keywords: diabetes mellitus, asthma, covid-19 vaccination, metabolic syndrome, comorbid, covid-19 obtained from Google Scholar, PubMed, ScienceDirect, Vaccine published between (2011-2023). The inclusion criteria in this study were patients with diabetes mellitus, comorbidities, and covid-19 vaccination. The exclusion criteria for this study were literature that was not available in full text, case reports. A total of 102 articles were identified, then filtered into 50 articles. Then after adjusting the inclusion criteria, 23 articles were obtained.

3 RESULTS AND DISCUSSION

The results of the systematic review obtained 23 research reports that can be used to answer the formulation of this research problem. Diabetes mellitus is one of the chronic diseases that is catastrophic because it has a high morbidity and mortality rate throughout the world, both in developed countries and in developing countries. This disease has become more important to pay attention to because of the COVID-19 pandemic, a viral infectious disease that mainly affects the respiratory tract.

Determining the amount of diabetes mellitus therapy requires HbA1C examination as a standard according to PERKENI 2021, namely, if HbA1C is below 7.5% and within 3 months HbA1C is above 7%, monotherapy is given. If within 3 months monotherapy does not reach the target below 7.5%, it is upgraded to a combination of 2 drugs with different modes of action. If within 3 months it has not reached the target, it is given a combination therapy of 3 drugs with different mechanisms of action or with additional insulin. If HbA1C is above 9% needs to be

given insulin (Endocrinology Society Indonesian.

Research by Fortuna et al (2023) with a total of 120 patients found that in the evaluation of diabetes mellitus treatment at Baptist Batu Hospital, there were problems with antidiabetic drugs such as ineffective drugs, patients should have received combination therapy, instead of receiving single therapy, then dose selection, inappropriate indication, dose. So that in the future more evaluation must be carried out regarding the selection of drugs, and doses and must be according to the right indications (Fortuna Surat Bala et al., 2023).

Research by Kuna et.al (2022) at the Gogagoman Health Center using descriptive methods retrospectively with the sampling method, namely total sampling of 81 people, found that the treatment of type 2 diabetes mellitus used metformin (61%), glimepiride (11%), glibenclamide (2%), metformin & glimepiride (11%), and a combination of metformin & glibenclamide (2%). The rationality of treatment for type 2 diabetes mellitus at the Gogagoman Health Center in 2022 was 34%. Based on the evaluation of antidiabetic treatment, 68% of patients had the right indication, 68% had the right drug, 69% had the right patient 75%, and 77% had the right dose. (Kuna et al., 2022).

Based on research by Meryta et al (2023) descriptive method with the number of prescriptions, namely 499 prescription sheets. Based on the class of drugs and active substances most widely used are the biguanid group (Metformin) as many as 13,356 tablets (68.62%), 3rd Generation Sulfonylurea Group (Glimepiride) as many as 3,232 tablets (16.61%), 2nd Generation Sulfonylurea Group (Glibenclamide) as many as 2,716 tablets (13.95%), Alpha Glucosidase Inhibitors (Acarbose) as many as 160 tablets (0.82%). (Meryta et.al, 2023).

This is in line with research with a retrospective method with a total of 97 patients. It was found that there were 97 subjects of Type 2 DM patients who received single and combination metformin therapy in 2019. Based on the data, the female gender with age 56-65 years is more and patients also have a diagnosis of DM with complications. The accuracy of prescribing based on research obtained the right indication based on the patient's BMI of 76.3%, and based on the doctor's diagnosis of 100%. Appropriate medication based on the dose of administration was 100%. The right patient condition was 97.94%. Overall evaluation of metformin prescribing has reached 75.26%. (Indah Cahyaningsih et al., 2021)

According to research by Bintang et.al (2021) in a cross-retrospective manner with a sample size of 64 patients, it was found that the most prescribed drug was a combination of oral antidiabetics, namely Gliklazid and Metformin (29.70%), in terms of the correct dose and the right way of administering the drug, it was by the guidelines in the Ministry of Health and FRS (100%), in data on patients who experienced a decrease in GDA, it was seen that the administration of sulfonylurea and biguanide combination therapy compared to single therapy was 92.5%. (Bintang et.al, 2021).

This is supported by a research article by Jonathan et al. (2019) with a total sample of 115 samples, the single oral antidiabetic therapy most widely used for the treatment of patients with type 2 diabetes mellitus at the Bandung City Hospital is metformin (43.5%). This is by the management of diabetes mellitus regulated by Perkeni 2021. Most cases of type 2 DM use metformin as first-line therapy (Jonathan et al., 2019). Metformin has the main effect of reducing liver glucose production (gluconeogenesis) and improving glucose uptake in peripheral tissues by 10-40% and can reduce HbA1C by 1-1.3%. In addition, metformin is safe, effective, and inexpensive, does not cause hypoglycemia compared to the sulfonylurea group, and can also reduce the incidence of CVD. However, metformin cannot be used in patients who have GFR < 30 mL/min. (Endocrinology Society Indonesian.

Treatment of patients with diabetes mellitus and stroke comorbidities at Aji Muhammad Parikesit Tenggarong Hospital with a total sample of 20 people, it was found that the most widely used antidiabetics were metformin monotherapy and combination therapy between metformin and glimepirid, In In In which In In In amounted to 15%. The combination of oral antidiabetic drugs is the right combination because it has a synergistic way of working that can reduce blood glucose more than every single treatment. In addition to the combination of oral drugs, oral-insulin combination therapy was also obtained, namely metformin with novorapid insulin. The use of insulin is given if the patient's condition has dropped or has high blood glucose levels. The widespread use of novorapid injection is because it is rapid-acting and can provide a faster postprandial glucose level reduction effect than regular insulin. (Octariani et al., 2022)..

As for the comorbid stroke itself, the therapy given is ARB hypertension drugs, namely candesartan by 20%. This is by Perkeni 2021. The use of aspirin antiplatelets (40%) is also important to reduce vascular risk, especially in the 24-48 hours of the attack. Aspirin is the most commonly used antiplatelet agent because it reduces recurrent vascular events from 22% to 13% and the risk of

recurrent stroke 15% compared to placebo (Octariani et al., 2018). (Octariani et al., 2022)..

Research by Inayah et.al (2016) in one of the hospitals in Pekanbaru with a total of 296 patients with diabetes mellitus with comorbid hypertension, found that the most widely used diabetes mellitus treatment was metformin by 90.3% and the smallest was acarbose by 1.69%. As for the treatment of comorbid hypertension, not all patients with type 2 DM with comorbid hypertension received OAH therapy, almost half of the subjects without antihypertensive drugs, namely 44.91%. This can occur because the subjects included in the study were those who had complete data at the first visit, so maybe the doctor had just diagnosed comorbid hypertension for the first time. So that this can be a consideration for doctors not to immediately provide OAH therapy because the management of type 2 DM patients with comorbid hypertension also begins with lifestyle modification. As for patients who received antihypertensive treatment therapy, the most widely used was candesartan at 66.24%. Candesartan administration has almost the same effect as ACE-I but has the advantage of not causing side effects of dry cough and angioedema. (Inayah et al., 2016).

Based on the research by Irene et.al (2020) with a cross-sectional, retrospective research design using a total of 115 samples. It was found that patients who used oral antidiabetics generally had used them <5 years (76.3%) and used monotherapy (63.5%). Neuropathy (42.6%) and hypertension (85.9%) were the most common complications and comorbidities of diabetes in this study. Tight glycemic control is an important management for people with diabetes mellitus. (Irene et al., 2020)

Pratama and Ratnasari's research at Denpasar Bali Private Hospital used a cross-sectional research design with a descriptive observational approach of 120 patients. It was found that the most widely used antidiabetics were the biguanid group (37.9%) with the type of drug metformin (37.9%). As many as 43.32% of patients received a combination of two antidiabetic therapies, namely biguanid and sulfonylurea groups with metformin and glimepiride. The most widely used pattern of use of other drugs is the vitamin group (41.48%) with the type of drug mecobalamin (40.37%). (Pratama and Ratnasari, 2021).

Based on research by Kardela et al. (2022) using a cross-sectional design, the number of subjects was 23 patients. The results of the evaluation of drug-related problems in 23 patients showed that there were two categories of drug-related problems identified, namely the problem of potential drug interactions of as many as 35 events (59%) and the problem of too high doses or frequencies as many as 24 events (41%). Based on the results of the assessment and identification of drug-related problems, it is necessary to prevent and manage drug-related problems in patients with type 2 diabetes mellitus with chronic renal failure. (Kardela et al., 2022).

Millah's research (2018) used a retrospective method with a sample size of 54 patients. It was found that the pattern of use of treatment for diabetic ulcers was the most given single antibiotic combination therapy and the combination of ceftriaxone + metronidazole. And obtained the results of the evaluation of the correct use of antibiotics for indications, the right drug, the right dose, the right way of administration, the right time interval, and the right duration of administration. (Millah, 2018).

Research by Ohsugi et.al (2021) with a total of 10,151 patients found that 6.6% of patients with diabetes mellitus had comorbidities, including Dyslipidemia (84.7%) and hypertension (75.1%) were the most common diseases, followed by chronic kidney disease (35.4%), retinopathy (23.1%), and cardiovascular disease (22.1%). Overall, 36.0% of patients were overweight/obese (body mass index 25 kg/m2) and 18.6% had a history of neoplasm. The prevalence of comorbid conditions/complications tends to increase with age and duration of type 2 diabetes mellitus (Ohsugi et al., 2021).

Meanwhile, according to research by Kuo et al (2015) with a total of 33,709 patients. Comorbidities found in DM patients include hypertension, hyperlipidemia, stroke, coronary artery disease, and/or kidney disease. The HR of dementia in diabetics increased from 1.41 in those with no comorbidities to 2.49 in those with ≥4 comorbidities. In the DM group, HRs were 1.22 for non-insulin users 1.41 for insulin users, and 1.49 for type 1 DM, and 1.23 for type 2 DM. Diabetic patients have an increased risk of dementia, and comorbidities increase this risk (Kuo et al., 2015).

DM patients who experience Acute Myocardial Infarction have worse in-hospital clinical outcomes than non-diabetic patients. There are important differences in DM type with patients with type 1 diabetes mellitus having worse outcomes overall and receiving less revascularization overall. (Sethupathi et al., 2023)..

Covid-19 patients with diabetes mellitus have a higher severity of infection such as experiencing cytokine storms to the risk of death. The use of antidiabetic drugs has a target activity on DPP4 which increases insulin secretion with DPP4 as an aminopeptidase on the cell membrane which plays a

role in various physiological processes including the immune response. Chronic hyperglycemia causes abnormal immune responses and not. This mechanism further increases the risk of death in COVID-19 patients with diabetes mellitus (Rahayu et al., 2021). The research of Nanda et al. (2021) from a total of 404 samples, shows the effect of diabetes mellitus on covid-19 and has a risk of being infected with Covid-19 of 0.307 times compared to patients without diabetes mellitus. High blood sugar will accelerate the replication of the coronavirus (Nanda et al., 2021). (Nanda et al., 2021).

Priscilla and Heri's research (2023) is an observational analytic study with a cross-sectional research design, which was conducted on 418 COVID-19 patients who were treated at Husada Hospital from January to December 2020. The results showed that the majority of COVID-19 patients with comorbid diabetes mellitus experienced severe/critical severity (61.4%) and the presence of comorbid diabetes mellitus increased the incidence of death in COVID-19 patients by 5.9 times (p-value <0.05). This study also found that age, use, insulin therapy, and the presence of other comorbidities also played a role in the worsening of the COVID-19 condition. (Erwani and Nofriandi, 2017)..

Based on research by Esfandiari et al. (2022) this study used descriptive-comparative research methods with a cross-sectional approach. Based on the results of this study, 71 respondents were obtained, the most respondents consisted of age> 45 years with a total of 50 patients (70.4%) the most respondents were women as many as 37 patients (52.1%). Patients without comorbidities were 44 people (62%). Covid-19 patients who recovered were more than Covid-19 patients who died, namely 59 patients (83.1%). In the results of statistical test analysis with Mann Whitney, the p-value = 0.000 (p <0.05) was obtained, which means that there is a significant difference in the recovery rate between COVID-19 patients who have comorbid diabetes mellitus and COVID-19 patients without comorbidities at Natar Medika Natar Hospital in 2021. (Esfandiari et al., 2022).

This is in line with the research of Mauricio et.al (2023) with a retrospective cohort design method using subjects totaling 1,238,710 subjects. It was found that diabetes mellitus was an independent risk factor for mortality in people with Covid-19. The number of fatal events decreased during the second and third waves in our region, both in people with diabetes and obesity (Mauricio et al., 2023).

In the research of Gouda et.al (2022) with a Cohort study research design. The total sample of 135 obtained the results of the study that SARS-CoV-2 vaccination in children and adolescents with type 1 diabetes is safe and not associated with glucose imbalance directly. (Gouda et al., 2022). Then there was a retrospective study with a total of 39 samples, it was found that no significant differences in glycemic control and glycemic index were observed at different times throughout the vaccination cycle and did not depend on the type of vaccine. (Piccini et al., 2022)

4 CONCLUSIONS

Based on systematic reviews that have been reviewed and reviewed, it is found that the treatment of diabetes mellitus mostly uses biguanide drugs (metformin) both as single and combination therapy. The most widely used treatment for comorbidities such as hypertension is candesartan, while for other comorbidities it is adjusted to the management guidelines. Evaluation of diabetes mellitus treatment with comorbidities is by the Perkeni 2021 management guidelines so there are no problems. Overall, it is appropriate, namely the right indication, the right drug, the right dose, the right method of administration, the right time interval, and the right duration of administration.

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