Journal Health of Indonesian
Volume 2, Number 02, March 2024 (No 77-86)
DOI 10.
E.SSN 2987-0313 (Online)

Type II Diabetes Mellitus And Anti-Diabetic Therapy Patterns In Hospital X, Central Java

Okky Intan Mawarni[1], Anak Agung Indah Krisnadewi[2], Elsa Mahardika Putri[3], Anis Akhwan Dhafin[4], Fendy Prasetyawan[5]
Universitas Kadiri, Kediri[1,2,3,4,5]

Article Info
Corresponding Author:
Okky Intan Mawarni
E-mail:
okkyintanm@unik-ac.id

ABSTRACT

Type 2 DM can be a risk factor for arteriosclerotic cardiovascular disease complications (coronary heart disease, stroke, and peripheral arterial disease), heart failure, chronic renal failure, and cardiovascular risk. This cross-sectional study was conducted on 100 type 2 diabetic patients who were prescribed anti-diabetic therapy. The prescription pattern was analyzed and adherence to treatment guidelines was done by comparing with the 2021 PERKENI guidelines. The results of the distribution of the characteristics of T2DM respondents at X Hospital 2022 were mostly aged> 45 years as much as 87%, the most gender was male as much as 54%, the most comorbidities were 97% of respondents, the most treatment pattern was monotherapy as much as 64%, the highest number of drugs received by patients was 81% with criteria> 5 drugs.
Keywords: theraphy pattern; diabete mellitus; T2DM.

INTRODUCTION

DM is a global health threat, which is a category of metabolic disease characterized by hyperglycemia that occurs due to abnormalities in insulin secretion, insulin performance, or both. Insulin resistance has been recognized as the cause of Type 2 DM (PERKENI, 2021). Based on the International Diabetes Federation(IDF, 2019). DM is a long-term (chronic) disease that is found when there is an increase in blood glucose levels due to insufficient insulin production in the pancreas or when insulin cannot be used efficiently by the body. The incidence of DM is estimated at 537 million adults aged 20-79 years worldwide 10.5% of all adults in this age category have DM. Based on estimates in 2021, by 2030 it is estimated that 643 million and by 2045 783 million adults aged 20-79 years could be living with DM (IDF, 2022).

The varying use of drug therapy (single oral antidiabetic therapy, combined antidiabetic therapy, single insulin therapy, and combined insulin therapy) will result in differences in the length of stay of a patient which is influenced by blood sugar levels and HbA1C so that an analysis is needed regarding the relationship between drug use patterns and the length of stay of patients with diabetes mellitus. (Versita et al., 2022).

Treatment patterns can be divided into monotherapy with the use of a single drug, combination therapy, and therapy of type 2 DM with comorbidities. The general pattern of use of antidiabetics is monotherapy (metformin; sulfonylurea/gained; alpha-glucosidase

inhibitor; thiazolidinedione; DPPV IV inhibitor; SGLT-2 inhibitor; GLP-1 agonist) for HbA1c <7.5%, combination of two drugs (sulfonylurea/gained; alpha-glucosidase inhibitor; thiazolidinedione; DPPV IV inhibitor; basal insulin; SGLT-2 inhibitor; GLP-1 agonist) as first-line with HbA1c ≥7.5% and a combination of three drugs as second-line (sulfonylurea/gained; alpha-glucosidase inhibitor; thiazolidinediones; dppv iv inhibitor; basal insulin; SGLT-2 inhibitor; GLP-1 agonist) with HbA1c ≥7.5%. Meanwhile, for HbA1c >9% with reduced clinical symptoms, a combination of 2/3 drugs with additional insulin is given. However, if clinical symptoms worsen, insulin or insulin identification is given. (PERKENI, 2021).

The prescription pattern was analyzed and adherence to treatment guidelines was done by comparing with the 2021 PERKENI guidelines. Factors affecting the complexity of a patient's drug regimen include changes in pharmacokinetic and pharmacodynamic properties of drugs, severity of disease stage, chronic diseases, drug interactions, polypharmacy, and ICU environment. (Chiang et al., 2021). The prescription pattern was analyzed and adherence to treatment guidelines was done by comparing with the 2021 PERKENI guidelines. Factors affecting the complexity of a patient's drug regimen include changes in pharmacokinetic and pharmacodynamic properties of drugs, severity of disease stage, chronic diseases, drug interactions, polypharmacy, and ICU environment.

METHODS

Analysis of treatment patterns was carried out by recording with a form that had been made, the data was classified based on the drug category used monotherapy, combination therapy, or therapy with comorbidities. Univariate SPSS analysis of treatment patterns (number) of type 2 DM patients.

RESULTS AND DISCUSSION

Mechanisms of Type II Diabetes Occurrence

Mechanism of action of Type 2 DM drugs according to Padhi et al., (2020) by reducing insulin secretion from β-cells of islets of Langerhans, resulting in increased glucagon secretion from α-cells of islets of Langerhans and increased glucose production in liver cells, then neurotransmitter dysfunction and insulin resistance in the brain that causes lipolysis, increased glucose reabsorption by the kidneys, There is a reduction in the effect of incretin in the small intestine and decreased or decreased glucose absorption by peripheral tissues such as skeletal muscle, liver, and adipose tissue is the occurrence of damage or removal of the pancreas, such as pancreatitis, pancreatic cancer, and trauma can damage beta cells or reduce them impact less insulin, resulting in diabetes. If the damaged pancreas is removed, diabetes will occur due to the loss of beta cells. (Kahn et al., 2014). Certain drugs can affect beta cells or cause impaired beta cell function, these drugs include niacin, certain diuretics, antiepileptic drugs, psychiatric drugs, and drugs to treat HIV, pentamides, glucocorticoids, diabetes drug intolerance, or even statins. (Kalra et al., 2011)Type 2 DM is an interaction of genetics and lifestyle factors that play a vital role, fat or obesity can increase the risk of disease.

Respondents in this study were 100 respondents, the number of respondents was calculated based on the Slovin formula. The frequency distribution of respondent characteristics can be seen in Table 1:

Table 1. Frequency Distribution of Respondent Characteristics at X Hospital in 2022

NO	Characteristic	Frequencies	Percentages
1	Age (years)		
	<45	13	13%
	>45	87	87%
2	Type of Gender		
	Male	54	54%
	Female	46	46%
3	Concomitant Diseases		
	Available	97	97%
	Not available	3	3%
4	LOS		
	<5 hari	62	62%
	>5 hari	34	36%
5	Therapeutic outcomes		
	Reached	100	100%
	Not achieved	0	0%

Oral anti-hyperglycemia drugs can be given as single or combination therapy, in emergencies with severe metabolic decompensation, for example: ketoacidosis, severe stress, rapid weight loss, or the presence of ketonuria. (PERKENI, 2015). An alternative definition for polypharmacy is the use of more drugs than medically necessary (Herdaningsih et al., 2016).

Drug polypharmacy is divided into 3 types, namely, duplication, opposition, and alteration. Duplication is when two drugs with the same effect are given simultaneously, it can increase the risk of side effects. Opposition is when two drugs with opposite effects are administered together, which can result in a decrease in the effectiveness of one or both drugs. Alteration is the change in the function or performance of absorption, distribution, metabolism, and excretion of a drug due to other drugs. The tendency of polypharmacy practices and the possibility of drug interactions is increasing. Oral anti-hyperglycemia drugs can be given as single or combination therapy, in emergencies with severe metabolic decompensation, for example: ketoacidosis, severe stress, rapid weight loss, or the presence of ketonuria. (PERKENI, 2015).

Data obtained based on the frequency of demographic distribution of patients, T2DM aged> 45 years as much as 87% (N: 100) which is more than the population aged under 45 years, this is generally influenced by physiological conditions and the presence of complications with comorbidities that have an impact on the worsening of the disease in the presence of diabetes. (Chen et al., 2023). Research by Chen, 2023 explains that the odds ratio of T2DM patients aged 50-59 is much higher than those under 50 years of age.

Males outnumbered females by 54% (N: 100) in this study, which is synergistic with the global prevalence that states that the T2DM population is predominantly male. The prevalence of type 2 diabetes is also characterized by gender differences. Gender differences in diabetes prevalence are related to reproductive life: that is, men have more diabetes before puberty, whereas women have more diabetes after menopause and in old age (IDF, 2021)

T2DM is prone to disease complications, in this study there were 97% of patients with comorbidities with severe disease severity, including most T2DM patients also experience acute or chronic complications (PERKENI, 2021) Hyperglycemia is associated with several potentially life-threatening microvascular and macrovascular complications, including heart failure, coronary artery disease (CAD) and chronic kidney disease (CKD). Due to these complications, diabetes poses a risk of reduced quality of life and a high economic burden, making it a critical chronic disease to address. (Soeatmadji et al., 2023).

The following are the classifications of oral diabetes by drug mechanism of action:

Treatment Patterns of T2DM Patients

The treatment pattern of T2DM respondents in this study can be divided into monotherapy and combination therapy, as shown in Table 2 below:

Table 2. Treatment Pattern Characteristics of T2DM Patients

NO	Characteristics	Frequencies	Percentage
1	Number of Drug Items received		
	<5 drugs	10	10%
	5 drugs	9	9%
	>5 drugs	81	81%%
2	Treatment Pattern		
	Monotherapy	64	64%
	Combination Therapy	36	36%

The number of drugs received by patients in this study is divided into three main classifications, namely, patients who received <5 drug items as much as 10%, 5 drug items as much as 9%, and >5 drug items as much as 81%. This is due to the critical condition at the time of admission varies greatly, and geriatric conditions are also a factor in patients receiving many drugs at one time. Type 2 diabetes mellitus (T2DM) is a cause of considerable polypharmacy, explained by the need to treat microvascular and macrovascular complications, but also due to the presence of comorbidity groups. Elderly diabetic patients are at particular risk for polypharmacy for various reasons: Multimorbidity (arterial hypertension, solid or hematologic malignancies, chronic heart failure, etc.), age-related pharmacokinetic variability in the setting of liver or kidney disease, lack of adherence (voluntary or involuntary-in psychiatric disorders), and others. In addition, elderly patients are more likely to use over-the-counter drugs and herbal supplements, which may lead to drug interactions (Annani-Akollor et al., 2019; Lipska et al., 2016; Mortazavi et al., 2016; Noale et al., 2016).

T2DM respondents in this study received T2DM therapy as follows:

Table 3. Drug Data of DMT2 Patients of RSDM X 2022

Therapy pattern	Drug Name	Amount	Percentage
Monotherapy			
Biguanide	Metformin	32	32%
Sulfonylureas	Glimepiride	1	1%
Alpha-glucosidase	Acarbose	1	1%

Therapy pattern	Drug Name	Amount	Percentage
	Human premixed : Ryzodeg		
Insulin	Analog rapid acting : Insulin aspart (Novorapid) Insulin glulisine (Apidra) Insulin lispo (Humalog)	30	30%
	Analog long acting : Insulin detemir (Levemir)		
Combination Therapy			
ADO	Sulfonilurea + alfaglucosidase inhibitor + biguanide + DPP4 inhibitor + biguanide+ SGLT2	7	7%
ADO+insulin	Biguanide + insulin aspart	21	21%
Insulin+insulin	Insulin aspart + insulin gargine + insulin premix + insulin detemir + insulin gluisin Insulin lispo + insulin detemir + insulin glargine	8	8%
TOTAL		100	100%

The use of monotherapy in this study was 64% combined therapy as much as 36%, this condition is due to T2DM being a secondary diagnosis, so blood sugar can still be controlled by giving monotherapy with metformin. Clinically, metformin is recommended as a first-line glucose-lowering therapy, along with lifestyle changes. The use of monotherapy is generally considered based on the first line of treatment for reasons of good treatment effectiveness, minimal hypoglycemia, safe to use for obese patients, improved cardio outcomes in respondents with heart disease, and cost-saving drug prices.

Meanwhile, the consideration of choosing combination therapy is generally related to the reason for the price of drugs that vary because most respondents with combination therapy are patients with duplicate comorbid diseases or T2DM as comorbid, so the drugs used vary in type and price. According to PERKENI, the first line used in combination therapy is low-dose metformin thiazolidinedione or acarbose. However, if the patient receives 3 drug combinations at the same time oral antihyperglycemic drugs whose output does not reach the therapeutic target can use a combination of insulin or a combination of DPP4 inhibitors or SGLT2 inhibitors.

The choice of metformin monotherapy as the main line according to instructions (American Diabetes Association, 2022), of various pharmacologic agents have been evaluated for diabetes prevention, and metformin has the strongest evidence base. First-

line therapy depends on comorbidities, patient-centered medicine factors, and management needs and generally includes metformin and comprehensive lifestyle modification. Other drugs (glucagon-like peptide 1 [GLP-1] receptor agonists, sodium-glucose cotransporter 2 [SGLT2] inhibitors), with or without metformin based on glycemic needs, are appropriate initial therapy for individuals with type 2 diabetes with or at high risk for atherosclerotic cardiovascular disease (ASCVD), HF, and/or chronic kidney disease (CKD). Metformin should be continued after initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits.

The use of monotherapy drugs in this study was dominated by metformin in the biguanide antidiabetic group. Metformin has periodic pharmacokinetics after digestion with a half-life of about 5 hours, absorbed by organic cation transporters without being metabolized in the body and widely distributed to various tissues such as the intestines, liver, and kidneys. The main route of elimination is through the kidneys. Metformin is contraindicated in patients with advanced renal insufficiency, indicated by a glomerular filtration rate (GFR) <30 mL/min/1.73 m2, if metformin is used when GFR is significantly reduced, the dose should be reduced and the patient should be advised to discontinue treatment if nausea, vomiting, and dehydration appear from other causes (to prevent ketoacidosis). It is important to assess renal function before starting treatment (Chaudhury et al., 2017)

Metformin has an excellent safety profile, although it can cause gastrointestinal disturbances including diarrhea, nausea, and dyspepsia in nearly 30% of subjects after initiation. The introduction of metformin at low doses often improves tolerance. Extended-release preparations rarely cause gastrointestinal problems. Very rarely, metformin may cause lactic acidosis, especially in subjects with severe renal insufficiency. Another potential problem arising from the use of metformin is the decrease in drug efficiency as diabetes progresses. Metformin is highly efficient when insulin production is sufficient; however, when diabetes reaches a state of β-cell failure and results in a type 1 phenotype, metformin loses its efficacy. Metformin may cause vitamin B12 and folic acid deficiency (Fogelman et al., 2017). This needs to be monitored, especially in elderly patients. Although very rare, in patients with metformin intolerance or contraindications, other initial oral class drugs can be used (Chaudhury et al., 2017)

As for insulin as monotherapy in research, the types of insulin used are rapid-acting analog (rapid-acting insulin) and long-acting analog (long-acting insulin). Rapid-acting analogs are commonly used as postprandial (after-meal) blood sugar control with an onset of 5-10 minutes, a peak of action of 1 to 2 hours, and a duration of action of 4-6 hours (PERKENI, 2022). In this study, rapid insulin was commonly used by patients with a history or diagnosis of CKD. Decreased renal function leads to prolongation of insulin half-life and decreased insulin requirements, patients with stage 4 to 5 CKD (eGFR,30 mL/min/1.73 m2) often have delayed gastric emptying; administration of rapid-acting insulin after meals can help to match the insulin peak with the timing of the postprandial blood glucose peak. Postprandial rapid-acting insulin with dose adjustment for the amount eaten may help patients with a wide range of food intake (Marathe et al., 2017).

Insulin aspart was also used as monotherapy in this study, insulin novorapid is a rapid-acting insulin that controls the target with use after meals to achieve blood glucose concentrations, or reduce blood glucose in response to blood glucose measurements (Melo et al., 2019). The total daily insulin dose is usually between 0.4 to 1 unit/kg per day,

divided into long-acting insulin and rapid-acting insulin, such as insulin aspart. The average dose regimen given in this study ranged from 4-4-4 iu sc to 14-14-14 iu sc, depending on the needs of the respondents. In T2DM, insulin aspart is commonly added for further glycemic control in addition to oral medications or long-acting insulin. The recommended starting dose for patients with type-2 diabetes mellitus can be one of the following options: 4 units per meal, 0.1 units/kg per meal, or 10% of the basal dose. If hemoglobin A1c is less than 8%, consider reducing the basal insulin dose when adding insulin aspart with meals (Melo et al., 2019)

The use of long-acting insulin in this study was necessary to successfully achieve blood sugar targets. When starting insulin treatment for T2DM, daily injections of long-acting insulin can be used to lower glucose levels. If needed, rapid-acting insulin can be added at mealtimes. The insulin dose should be chosen carefully as too much insulin can result in life-threatening low blood glucose concentrations. To avoid overdose, a long iterative process called titration is used to gradually increase the amount of long-acting insulin injected so that the fasting glucose concentration reaches the normal range. Based on the self-measured fasting blood glucose (SMBG) value, the patient adjusts the daily insulin dose until the desired glucose concentration is achieved. This can take several months. Unfortunately, many patients never reach the treatment goal as the burdensome task of titration and lack of confidence in the medication can lead to adherence issues (Arnolds et al., 2013; Khunti et al., 2020)

The most common combination therapy in this study was with metformin and insulin aspart as much as 22%, which insulin aspart is a human insulin analog with the mechanism of inhibiting liver glycogen synthesis and promoting blood glucose absorption, thereby normalizing blood glucose levels (Fullerton et al., 2018). However, insulin aspart has some disadvantages such as rapid elimination speed and short mean residence time, metformin reduces blood glucose levels, lowers body weight, and protects cardiovascular health in T2DM patients (Zhao et al., 2022)

In the research conducted by Zhao et al., (2022) miglitol and metformin were combined with insulin aspart, and their effectiveness and reliability in the treatment of T2DM were compared the results showed that treatment with a combination of miglitol and insulin aspart is suitable for T2DM patients whose blood sugar levels are not under control, while combined treatment with metformin and insulin aspart is more suitable for patients who want to lower blood sugar and blood fat through weight loss, and patients with cardiac and renal insufficiency. While research by Zhao et al., (2022) explained that metformin combined with insulin aspart to treat gestational DM and chronic hypertension can effectively control blood glucose and blood pressure levels and reduce the risk of adverse perinatal and neonatal outcomes, which provides a positive effect on clinical treatment.

Another combination therapy of 2% was the use of insulin lispro with insulin glargine, 2% sulfonylurea, alpha-glucosidase, and 2% for combination therapy of insulin glargine and premix. Research by Candido et al., (2018) insulin glargine plus insulin lispro provided better glycemic control than insulin NPH plus RHI, as indicated by a significantly lower HbA1c after 16 weeks of treatment, along with an 8% lower 24-hour blood glucose AUC (p=0.037). In addition, the symptomatic rate of nocturnal hypoglycemia was 44% lower with insulin glargine plus insulin lispro compared to the comparator regimen (0.66 vs 1.18 episodes/month; p=0.001). (Ashwell et al., 2008). In addition, recipients of insulin analog

therapy reported greater satisfaction with treatment (Ashwell et al., 2008). plus insulin RHI or NPH plus insulin lispro. Insulin glargine plus insulin lispro provided better fasting blood glucose and/or HbA1c control than insulin NPH plus insulin lispro, and similar glycemic control to insulin glargine plus RHI. (Brunetti et al., 2010). Half of these studies also found that BBT with insulin glargine plus insulin lispro reduced the frequency of total nocturnal hypoglycemia or severe nocturnal hypoglycemia (Fulcher et al., 2005) versus NPH insulin plus insulin lispro (mean not turn hypoglycemia episodes per month). 1.2-2.0 vs. 3.2-3.6

Research conducted by Soeatmadji et al., (2023), About 36.7% of patients started single therapy and 13.6% of patients underwent combination therapy, more than 70% of patients used metformin and/or sulfonylurea as first-line treatment. The use of combination therapy with metformin and sulfonylurea was the most frequently used second-line therapy, followed by triple combination therapy with metformin, sulfonylurea, and dipeptidyl peptidase-4 inhibitors (DPP-4i). About 26.7% of patients used second-line therapy for 11.3%. During the follow-up period, only 22.7% of patients remained on monotherapy. The most frequently cited reason for switching from first-line to second-line therapy was due to treatment failure. The choice for second-line therapy was based on improved efficacy. Sulfonylureas were the most frequently discontinued treatment at all follow-up time points, accounting for 6.7%, 8.7%, 8%, and 8.4% of the population at 6, 12, 24, and 36 months, respectively, followed by metformin and fixed-dose metformin + DPP-4i.

CONCLUSION

The results of the distribution of the characteristics of T2DM respondents in XSurakarta Hospital 2022 were mostly aged> 45 years as much as 87%, the most gender was male as much as 54%, the most comorbidities were 97% of respondents, the most treatment pattern was monotherapy as much as 64%, the highest number of drugs received by patients was 81% with the criteria> 5 drugs.

REFERENCE

American Diabetes Association. (2022). Standards of Medical Care in Diabetes - Abridged for Primary Care Providers. *Clinical Diabetes*, *40*(1), 10–38. https://doi.org/10.2337/cd22-as01

Annani-Akollor, M. E., Addai-Mensah, O., Fondjo, L. A., Sallah, L., Owiredu, E.-W., Acheampong, E., & Akamugri, S. (2019). Predominant Complications of Type 2 Diabetes in Kumasi: A 4-Year Retrospective Cross-Sectional Study at a Teaching Hospital in Ghana. *Medicina*, *55*(5), 125. https://doi.org/10.3390/medicina55050125

Ashwell, S. G., Bradley, C., Stephens, J. W., Witthaus, E., & Home, P. D. (2008). Treatment Satisfaction and Quality of Life With Insulin Glargine Plus Insulin Lispro Compared With NPH Insulin Plus Unmodified Human Insulin in Individuals With Type 1 Diabetes. *Diabetes Care*, *31*(6), 1112–1117. https://doi.org/10.2337/dc07-1183

Brunetti, P., Muggeo, M., Cattin, L., Arcangeli, A., Pozzilli, P., Provenzano, V., Francesconi, A., Calatola, P., & Santeusanio, F. (2010). Incidence of severe nocturnal hypoglycemia in patients with type 1 diabetes treated with insulin lispro or regular human insulin in addition to basal insulin glargine. *Nutrition, Metabolism and Cardiovascular Diseases*, *20*(7), 519–526. https://doi.org/10.1016/j.numecd.2009.05.007

Camire, E., Moyen, E., & Stelfox, H. T. (2009). Medication errors in critical care: risk factors, prevention and disclosure. *Canadian Medical Association Journal*, *180*(9), 936–943. https://doi.org/10.1503/cmaj.080869

Candido, R., Wyne, K., & Romoli, E. (2018). A Review of Basal-Bolus Therapy Using Insulin Glargine and Insulin Lispro in the Management of Diabetes Mellitus. *Diabetes Therapy*, *9*(3), 927–949. https://doi.org/10.1007/s13300-018-0422-4

Chaudhury, A., Duvoor, C., Reddy Dendi, V. S., Kraleti, S., Chada, A., Ravilla, R., Marco, A., Shekhawat, N. S., Montales, M. T., Kuriakose, K., Sasapu, A., Beebe, A., Patil, N., Musham, C. K., Lohani, G. P., & Mirza, W. (2017). Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. *Frontiers in Endocrinology*, *8*. https://doi.org/10.3389/fendo.2017.00006

Chen, M., Wang, Y., Feng, P., Liang, Y., Liu, Q., Yang, M., Lu, C., Shi, P., Cheng, J., Ji, A., & Zheng, Q. (2023). Association between Age at Type 2 Diabetes Onset and Diabetic Retinopathy: A Double-Center Retrospective Study. *Journal of Diabetes Research*, *2023*. https://doi.org/10.1155/2023/5919468

Chiang, L., Huang, Y., & Tsai, T. (2021). Clinical pharmacy interventions in intensive care unit patients. *Journal of Clinical Pharmacy and Therapeutics*, *46*(1), 128–133. https://doi.org/10.1111/jcpt.13265

de Souza, K. Irfan, F. Masud, & M.W. Saif. (2016). Diabetes Type 2 and Pancreatic Cancer: A History Unfolding. *JOP*, 144–148.

Diabetes. (2020). *Corticosteroids are used to reduce harmful inflammation but can lead to diabetes - often referred to as steroid diabetes*. https://www.diabetes.co.uk/drug-induced-diabetes.html

Endokrinologi Indonesia PEDOMAN PENGELOLAAN DAN PENCEGAHAN DIABETES MELITUS TIPE, P. (n.d.). *PEDOMAN PENGELOLAAN DAN PENCEGAHAN DIABETES MELITUS TIPE 2 DEWASA DI INDONESIA-2021 PERKENI i Penerbit PB. PERKENI*.

Ewald, N. (2013). Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. *World Journal of Gastroenterology*, *19*(42), 7276. https://doi.org/10.3748/wjg.v19.i42.7276

Fogelman, Y., Kitai, E., Blumberg, G., Golan-Cohen, A., Rapoport, M., & Carmeli, E. (2017). Vitamin B12 screening in metformin-treated diabetics in primary care: were elderly patients less likely to be tested? *Aging Clinical and Experimental Research*, *29*(2), 135–139. https://doi.org/10.1007/s40520-016-0546-1

Fulcher, G. R., Gilbert, R. E., & Yue, D. K. (2005). Glargine is superior to neutral protamine Hagedorn for improving glycated haemoglobin and fasting blood glucose levels during intensive insulin therapy. *Internal Medicine Journal*, *35*(9), 536–542. https://doi.org/10.1111/j.1445-5994.2005.00902.x

Fullerton, B., Siebenhofer, A., Jeitler, K., Horvath, K., Semlitsch, T., Berghold, A., & Gerlach, F. M. (2018). Short-acting insulin analogues versus regular human insulin for adult, non-pregnant persons with type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD013228

Herdaningsih, S., Muhtadi, A., Lestari, K., & Annisa, N. (2016). Potential of Drug-Drug Interaction in Polypharmacy Prescription: Retrospective Study on a Drugstore in Bandung. *Indonesian Journal of Clinical Pharmacy*, *5*(4), 288–292. https://doi.org/10.15416/ijcp.2016.5.4.288

International Diabetes Federation (IDF) 9th Atlas. (2019). *International Diabetes Federation*. https://diabetesatlas.org/atlas/ninth-edition/

International Diabetes Federation. (2021). *IDF Diabetes Atlas, 10th edn*.

International Diabetes Federation. (2022). *IDF Diabetes Atlas 2022 Reports*. IDF Diabetes Atlas 2022 Reports. https://diabetesatlas.org/2022-reports/

Kalra, S., Kalra, B., Agrawal, N., & Unnikrishnan, A. (2011). Understanding diabetes in patients with HIV/AIDS. *Diabetology & Metabolic Syndrome*, *3*(1), 2. https://doi.org/10.1186/1758-5996-3-2

Khunti, K., Giorgino, F., Berard, L., Mauricio, D., & Harris, S. B. (2020). The importance of the initial period of basal insulin titration in people with diabetes. *Diabetes, Obesity and Metabolism*, *22*(5), 722–733. https://doi.org/10.1111/dom.13946

Lipska, K. J., Krumholz, H., Soones, T., & Lee, S. J. (2016). Polypharmacy in the Aging Patient. *JAMA*, *315*(10), 1034. https://doi.org/10.1001/jama.2016.0299

Marathe, P. H., Gao, H. X., & Close, K. L. (2017). American Diabetes Association Standards of Medical Care in Diabetes 2017. *Journal of Diabetes*, *9*(4), 320–324. https://doi.org/10.1111/1753-0407.12524

Melo, K. F. S., Bahia, L. R., Pasinato, B., Porfirio, G. J. M., Martimbianco, A. L., Riera, R., Calliari, L. E. P., Minicucci, W. J., Turatti, L. A. A., Pedrosa, H. C., & Schaan, B. D. (2019). Short-acting insulin analogues versus regular human insulin on postprandial glucose and hypoglycemia in type 1 diabetes mellitus: a systematic review and meta-analysis. *Diabetology & Metabolic Syndrome*, *11*(1), 2. https://doi.org/10.1186/s13098-018-0397-3

Noale, M., Veronese, N., Cavallo Perin, P., Pilotto, A., Tiengo, A., Crepaldi, G., & Maggi, S. (2016). Polypharmacy in elderly patients with type 2 diabetes receiving oral antidiabetic treatment. *Acta Diabetologica*, *53*(2), 323–330. https://doi.org/10.1007/s00592-015-0790-4

Padhi, S., Nayak, A. K., & Behera, A. (2020). Type II diabetes mellitus: a review on recent drug based therapeutics. In *Biomedicine and Pharmacotherapy* (Vol. 131). Elsevier Masson SAS. https://doi.org/10.1016/j.biopha.2020.110708

PERKENI. (2015). *Konsensus Pegendalian dan Pencegahan Diabetes mellitus Tipe 2 di Indonesia* . PERKENI.

S.E. Kahn, M.E. Cooper, & S.D. Prato. (2014). Pathophysiology and Treatment of Type 2 Diabetes: Perspectives on the Past, Present and Future. *Lancet* , *383*, 1068–1083.

Soeatmadji, D. W., Rosandi, R., Saraswati, M. R., Sibarani, R. P., & Tarigan, W. O. (2023). Clinicodemographic Profile and Outcomes of Type 2 Diabetes Mellitus in the Indonesian Cohort of DISCOVER: A 3-Year Prospective Cohort Study. *Journal of the ASEAN Federation of Endocrine Societies*, *38*(1), 68–74. https://doi.org/10.15605/jafes.038.01.10

Versita, R., Handayani, D., & Adiningsih, R. (2022). Relationship Patterns Of Medicine Use On The Long Of Treatment In Diabetes Mellitus Patient. In *Medical Sains : Jurnal Ilmiah Kefarmasian* (Vol. 7, Issue 4).

Zhao, Q., Li, H., Ni, Q., Dai, Y., Zheng, Q., Wang, Y., Ke, T., Li, L., Zhao, D., Dong, Q., Ji, B., Shi, J., Peng, Y., Zhang, Y., Xu, F., & Wang, W. (2022). Follow-up frequency and clinical outcomes in patients with type 2 diabetes: A prospective analysis based on multicenter real-world data. *Journal of Diabetes*, *14*(5), 306–314. https://doi.org/10.1111/1753-0407.13271