Glycemic Control Comparative of Metformin and Glimepiride in Monotherapy of Type 2 Diabetes Mellitus Patient at Islamic Jemursari Hospital Surabaya in 2018

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Abstract

Introduction: *Type 2 diabetes mellitus is caused by decreased tissue sensitivity to insulin. The prevalence of diabetes in the world has almost doubled since 1980, from 4.7% to 8.5% in adult population. Early diagnosis and treatment aimed at normalizing glycemic control are very important. The objective of this study was to evaluate and compare glycemic control of metformin and glimepiride in monotherapy of type 2 diabetes mellitus patients at Islamic Jemursari Hospital Surabaya.*
Method: *This was a retrospective observational study using secondary data (medical record), include glycemic control (RPG) before and two months after receiving therapy of outpatients' type 2 diabetes mellitus with metformin or glimepiride therapy in 2018. 96 samples were found that fit the inclusion criteria. The data were analyzed by Mann-Whitney test.*
Result: *Most patients were female, aged 50-69 years old, and dosage of metformin therapy 1500 mg/day or glimepiride therapy 2 mg/day. There was no significant difference ($p>0.05$) of glycemic control (RPG) of metformin compared to glimepiride therapies in type 2 diabetes mellitus patients at Islamic Jemursari Hospital Surabaya in 2018.*
Conclusion: *Metformin and glimepiride were not significantly different in glycemic control (RPG). There were patients with RPG >200 mg/dl after two months of metformin or glimepiride therapy.*

Keywords*: glimepiride, glycemic control, metformin, random plasma glucose, type 2 diabetes mellitus*

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Perbedaan Kontrol Glikemik Terapi Metformin Dibandingkan Glimepiride pada Pasien Diabetes Melitus Tipe 2 di RSI Jemursari Surabaya pada Tahun 2018

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Abstrak

Pendahuluan: *Diabetes melitus tipe 2 disebabkan oleh penurunan sensitivitas jaringan terhadap insulin. Prevalensi diabetes di dunia telah meningkat hampir dua kali lipat sejak tahun 1980, dari 4,7% menjadi 8,5% pada populasi dewasa. Diagnosis dan pengobatan dini yang bertujuan untuk menormalkan kontrol glikemik sangat penting. Penelitian ini bertujuan untuk mengevaluasi dan membandingkan kontrol glikemik monoterapi metformin dan glimepiride pada pasien diabetes melitus tipe 2 di RSI Jemursari Surabaya.*
Metode: *Desain penelitian ini adalah analisis observasional retrospektif (rekam medis), meliputi kontrol glikemik (GDS) pasien diabetes melitus tipe 2 (rawat jalan) dengan terapi metformin atau glimepiride sebelum terapi dan dua bulan setelah mendapatkan terapi. Pada pengumpulan data didapatkan 96 sampel yang sesuai dengan kriteria inklusi. Data yang didapatkan dianalisis dengan uji Mann-whitney.*
Hasil: *Mayoritas pasien adalah perempuan, berusia 50-69 tahun, dan mendapatkan dosis terapi metformin 1500 mg/hari atau glimepiride 2 mg/hari. Tidak terdapat perbedaan bermakna (p>0,05) pada kontrol glikemik (GDS) terapi metformin dibandingkan glimepiride pada pasien diabetes melitus tipe 2 di RSI Jemursari, Surabaya pada tahun 2018.*
Kesimpulan: *Tidak terdapat perbedaan bermakna pada glikemik kontrol (GDS) terapi metformin dan glimepiride. Terdapat pasien dengan GDS >200 mg/dl setelah 2 bulan terapi metformin atau glimepiride.*

Kata Kunci*: glimepiride, kontrol glikemik, metformin, glukosa darah sewaktu diabetes melitus tipe 2*

Introduction

Diabetes mellitus is a disease that is commonly found in society. It is also known as the mother of various diseases, due to various kinds of mild to severe complications which may occur. Type 2 diabetes mellitus occurs when the body experiences insulin resistance. Insulin resistance is considered as an important factor of metabolic disease or also known as metabolic syndrome.[1] The prevalence of diabetes mellitus in the world has almost doubled since 1980, from 4.7% to 8.5% in the adult population.[2] Treatment of type 2 diabetes mellitus include nonpharmacological and pharmacological therapy. Pharmacological therapy for patients with type 2 diabetes mellitus varies from the injection of insulin and oral anti-diabetic drug. Metformin and sulfonylureas are two of the many oral anti-diabetic drugs. Metformin works indirectly on insulin by inhibiting the process of gluconeogenesis while sulfonylureas have the main effect of increasing insulin secretion by pancreatic beta cells.[3]

Glycemic control can be monitored based on hemoglobin A1C values, FPG (Fasting Plasma Glucose), PPG (Post Prandial Glucose) and RPG (Random Plasma Glucose). RPG is the most feasible test because sampling is timeless, the availability of standardized tests is easy and inexpensive. Various studies have shown an acceptable correlation between HbA1C and RPG levels.[4] A1C of 7% is equivalent to a mean RPG of 154 mg/dl. A1C of 7 - 7.49% is equivalent to mean FPG or before meals 152 mg/dl or PPG average 176 mg/dl. A1C of > 9% is equivalent to the average RPG ≥212 mg/dl. Research on glycemic control differences between metformin compared to glimepiride therapies in type 2 diabetes mellitus patients at Islamic Jemursari Hospital Surabaya in 2018 has never been studied before. It is hoped that the results of this study can be taken into consideration in determining the type of oral anti-diabetic drug

used in type 2 diabetes mellitus.

Method

The design of this study was a retrospective observational analysis using secondary data (medical record). The medical record data included glycemic control (RPG) of outpatients' type 2 diabetes mellitus with metformin or glimepiride therapy before and two months after receiving therapy. Sampling was carried out using a purposive technique based on the size of the sample that was calculated based on inclusion and exclusion criteria. Population of this study was the entire medical record of adult (≥40 years) outpatients with type 2 diabetes mellitus at Islamic Jemursari Hospital Surabaya in 2018.

The dependent variable in this study is the glycemic control of type 2 diabetes mellitus patients (RPG). The independent variable in this study was metformin / glimepiride therapy given to patients with type 2 diabetes mellitus. Data analysis was performed using SPSS 26.0 software. The Mann-Whitney test was used to analyze glycemic control differences between metformin compared to glimepiride therapies.

Result

Ninety-six samples were found to fit the criteria (48 patients with metformin therapy and 48 patients with glimepiride therapy) who were treated from January-December 2018 at Islamic Jemursari Hospital Surabaya. Distribution and frequency of outpatients with type 2 diabetes mellitus who received metformin or glimepiride therapy based on sociodemographic characteristics are shown in table 1.

Table 1. Sociodemographic Characteristics of Subject

Sociodemographic Characteristics	Oral Antidiabetic Drug Group	
	Metformin	Glimepiride
Age (years)		
40-49	4	3
50-59	17	12
60-69	14	20
70-79	13	11
80-89	0	2
Gender		
Male	18	13
Female	30	35

There were 48 patients with metformin therapy with 18 male and 30 female patients. Meanwhile, there were 48 patients in glimepiride therapy group with 13 male and 35 female patients. The majority of patients who receiving metformin therapy were in a group aged between 50-59 years old. Meanwhile, patients with glimepiride therapy were in a group aged between 60-69 years old. Based on table 2, most patients received dosage of 1500 mg/day on metformin therapy and 2 mg/day on glimepiride therapy.

Table 2. Dosage of Metformin or Glimepiride Therapy

Dosage (mg/day)	n
Metformin	
500 mg/day	12
1000 mg/day	11
1500 mg/day	25
Glimepiride	
1 mg/day	13
2 mg/day	15
3 mg/day	8
4 mg/day	12

Random plasma glucose (RPG) of patients before receiving metformin therapy ranged from 83 to 260 mg/dl with an average of 146 mg/dl. Then, after two months therapy, RPG ranged from 77 to 242 mg/dl with an average of 144 mg/dl. No patient experienced hypoglycemia while receiving metformin therapy 500-1500 mg/day. RPG approaching the lower limit is possibly due to blood sampling done before the patient consumes food (table 3).

Random plasma glucose (RPG) of patients before receiving glimepiride therapy ranged from 78 to 352 mg/dl with an average of 186 mg/dl (table 4). After two months, RPG ranged from 97 to 307 mg/dl with an average of 167 mg/dl. RPG approaching the lower limit is posibbly due to blood sampling done before the patient consumes food. There were two patients aged over 80 years old. The first patient aged 81 years with RPG before receiving glimepiride therapy 2 mg/day was 190 mg/dl and two months after therapy was 118 mg/dl. The second patient aged 83 years with RPG before and after was 157 and 174 mg/dl consecutively.

RPG data of metformin or glimepiride therapy were not normally distributed (Shapiro Wilk test), then analyzed by Mann-Whitney test.

Table 3. Glycemic Control of Metformin Therapy

RPG	n	Minimum	Maximum	Average
Before therapy	48	83 mg/dl	260 mg/dl	146 mg/dl
Two months after	48	77 mg/dl	242 mg/dl	144 mg/dl

Table 4. Glycemic Control of Glimepiride Therapy

RPG	n	Minimum	Maximum	Average
Before therapy	48	78 mg/dl	352 mg/dl	186 mg/dl
Two months after	48	97 mg/dl	307 mg/dl	167 mg/dl

Table 5. Glycemic Control Between Metformin and Glimepiride Therapies

	OAD	n	SD	Median	Minimum	Maximum	*p*
ΔRPG	Metformin	48	48,708	,00	-95	116	0,218
	Glimepiride	48	51,239	-17,50	-131	57	

There was no significant different of glycemic control (ΔRPG) metformin compared to glimepiride therapies in type 2 diabetes mellitus patients with a p value of 0,218.

Discussion

Diabetes is found in every population in the world. The number of people with diabetes is steadily rising. An estimated 463.0 million adults aged 20–79 years worldwide have diabetes and 79.4% live in low- and middle-income countries.5 Based on the 2019 estimates, by 2030 a projected 578.4 million, and by 2045, 700.2 million adults aged 20–79 years, will be living with diabetes.[5] High blood glucose causes almost 4 million deaths each year,2 and the IDF estimates that the annual global health care spending on diabetes among adults was US$ 850 billion in 2017.[6] T2DM accounts for 90 - 95% of diabetes, with highest proportions in low- and middle-income countries. T2DM is most common in adults, but an increasing number of children and adolescents are also affected.[2] In 2019, the countries with the largest numbers of adults with diabetes are China, India and the United States of America, and are anticipated to remain so until 2030. Indonesia ranks 7th with a prevalence of 10.7 million people.[3,5] The Prevalence of diabetes mellitus worldwide is lowest among adults aged 20–24 years (1.4% in 2019). Among adults aged 75–79 years diabetes prevalence is estimated to be 19.9% in 2019 and predicted to rise to 20.4% and 20.5% in 2030, and 2045.[5] The prevalence of diabetes mellitus in Indonesia based on a doctor's diagnosis in the population aged ≥15 years was found to increase to 2% from 2013 to 2018 with the lowest in NTT, which was 0.9%, while the highest DM prevalence in DKI Jakarta was 3.4 %.[7] People with diabetes mellitus in Indonesia are more female (1.8%) than male (1.2%).[7] Based on age category, most patients are in the age range of 55-64 years and 65-74 years.[8] Most patient in this study were in age range of 50-59 years and 60-69 years which means according to the data above.

Metformin, one of oral anti-diabetic drug, is the preferred first-line medication for management of type 2 diabetes mellitus and prediabetes, is available as an immediate-release (IR) formulation and an extended-release (XR) formulation, both formulations are well tolerated and are effective in reducing A1C levels versus placebo in patients with type 2 diabetes mellitus. Patients treated with low doses of metformin are less likely to derive full benefit from it and ultimately may fail to achieve/maintain desired glycemic targets. While many patients need to start metformin at a lower dose and gradually increase it so as to minimize gastrointestinal side effects.[9] In conclusion, the results of the present study show that the efficacy of high-dose metformin is dose-dependent in Japanese patients with type 2 diabetes and the efficacy and safety of metformin were similar when taken either twice daily or three times daily.[10] There were

82 type 2 diabetes mellitus patients with prescribed 500 mg metformin twice daily. Type 2 diabetes mellitus patients which showed that both age and BMI were not the covariates influencing the efficacy of oral anti-diabetic drug. Therefore, obese and non-obese Type 2 diabetes mellitus patients would derive an equal benefit of metformin monotherapy.10 Meanwhile, the longer duration of administration of metformin will result in lower final FPG.[11]

Glimepiride is a sulfonylurea-based third-generation drug associated with a lower risk of hypoglycemia than other sulfonylurea.[12] Research conducted by Davis in 2004 proved that glimepiride has been found to effectively reduced FPG and PPG levels and A1C concentration and has a good safety profile.[13] 172 type 2 diabetes mellitus patients (M/F = 80/92), in whom glycemic control had been inadequate (HbA1C>7.0%) with a conventional SU (either gliclazide or glibenclamide) for at least 6 months, all subjects were randomly assigned to the 3rd sulfonylurea group whose sulfonylurea treatments were switched to glimepiride, or the 2nd sulfonylurea group whose treatments were not changed and the mean dosages of glimepiride were increased (initial 2.57 mg, final 3.21 mg) during the study period, this study prove that 6 month replacement of conventional SUs with glimepiride reduced insulin resistance, and glimepiride was more effective in obese than in non-obese Japanese diabetic patients.[14]

Eighty-five people with type 2 diabetes mellitus at the Jayabaru Public Health Center, Banda Aceh was performed blood tests in a standardized laboratory in the city of Banda Aceh. The results of the study show that out of 85 type 2 diabetes mellitus sufferers, most have inadequate glycemic control and they are mostly women, old age, low education, no work and long-term type 2 diabetes mellitus for 1-5 years.[15] Other factors contributing to deterioration of glycemic control on metformin therapy were lower education level, lower annual household income, and non-White/Caucasian race/ethnicity.[16] To prevent further complications, routine glycemic control is needed by sufferers.[15] Besides RPG, Glycemic control can be monitored based on hemoglobin A1C values, FPG (Fasting Plasma Glucose), PPG (Post Prandial Glucose). For decades, A1C level has been the dominant metric in assessing glycemic control. The A1C level is used by physicians and patients to evaluate treatment responses and optimize diabetes therapy, and in clinical type 2 diabetes mellitus research, it is the primary outcome of efficacy. However, A1C level has certain shortcomings as a measure of treatment benefit the most prominent being its limited responsiveness to blood glucose fluctuations then glycemic goals set on lowering A1C alone could result in unbalanced treatment adjustments, potentially increasing the risk for hypoglycemia.[17]

Forty-six men with type 2 diabetes of varying ages (45–70 years old) participated in the study, they were chosen because their AIC concentrations were >7.5% on two successive visits at intervals of 3–4 months while receiving glimepiride alone, 8 mg, or metformin alone, 2500 mg or both drugs, 8 and 2500 mg, respectively.[12] They were required to perform glucose testing four times a day prior to each meal and at bedtime, or at any time if they experienced symptoms of hypoglycemia; this study suggests that the insulin-lowering effect of glimepiride might be similar but slightly greater than metformin in subjects with comparable demographic characteristics.[12]

In another study also mentioned that the use of glimepiride/ metformin 1/500 mg twice daily as an oral anti-diabetic drug in combination therapy with insulin glargine will likely yield better outcomes than use of glimepiride four times a day in the treatment of type 2 diabetes mellitus patients with inadequate glycemic control.[18] This study did not analyze glycemic control based on the therapeutic dose received by the patient and did not analyze other factors that were thought to affect the patient's glycemic control, including BMI, medication adherence, diet, physical activity, etc.

Conclusion

Metformin and glimepiride were not significantly different in glycemic control (RPG). There were patients with RPG >200 mg/dl after two months of metformin or glimepiride therapy. It is estimated that there are other factors can affect the glycemic control of patients' RPG, suggesting that patients and doctors optimize nonpharmacological and pharmacological therapies, and also pay attention to other factors that can affect therapy, in controlling blood glucose levels.

Conflict of Interest

The authors report no conflicts of interest.

Acknowledgment

The authors would like to thank the patients and clinicians in the internal medicine department of Islamic Jemursari Hospital, Surabaya.

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