An evaluation of type 2 diabetes mellitus patients on different oral antidiabetic medications with regard to glycemic control and diabetic complications

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Abstract

Objective: Diabetes Mellitus is a chronic and progressive disease that significantly impairs the workforce and economy due to its complications. This study aims to evaluate patients diagnosed with type 2 diabetes mellitus who use different oral antidiabetic medications with regard to glycemic control and diabetic complications.

Materials and Methods: This study included 200 patients who were being followed-up for a diagnosis of Type 2 DM.

Results: Of the 200 patients included in the study, 131 were on metformin monotherapy and 69 were on metformin and gliclazide combination therapy. HbA1c value of Metformin monotherapy prescribed patients was 7,6%±1,5, metformin+gliclazide prescribed patients was 8,2%±1,9. There was a statistically significant difference between the two groups in terms of blood glucose levels (p<0.05). There was no significant difference between the two groups with regard to microvascular complications and body mass index.

Conclusion: Our study determined that the level of glycemic control manifested by Type 2 DM patients was suboptimal despite using different types of oral antidiabetics and that their body mass indices were high. We reached the conclusion that the present situation is linked to factors such as incorrect dietary habits, inadequate exercise and walking, failure to comply with the medical treatment suggested by the physician, and lack of awareness about the severity of the disease.

Keywords: diabetes mellitus, metformin, gliclazide

Introduction

The International Diabetes Foundation (IDF) estimates that at least 425 million individuals around the world suffer from diabetes (1). From 1980 to 2014, the standardized global prevalence of adult diabetes has doubled among males and increased by almost 60% in females. If these trends persist, the World Health Organization (WHO) target of halting the rise in the prevalence of diabetes by 2025 will not be achieved (2). The increase in the prevalence of diabetes challenges individuals, families, and health systems globally. Besides being associated with a significant mortality rate, type 2 diabetes mellitus (T2DM) is a chronic disease that can lead to serious comorbid conditions (3).

Type 1 diabetes is an autoimmune disease and depends on the destruction of insulin producer pancreatic beta cells. Type 1 DM generally observes at young..

Type 2 diabetes, insulin resistance and pancreatic beta cells It occurs as a result of the coexistence of the disorder seen in insulin secretion (4).

Insulin offers high effectiveness in the treatment of diabetes, however, the fact that it cannot be used orally poses a significant problem and reduces patient compliance with treatment. For this reason, numerous studies have been conducted to discover oral antidiabetic medications; and the first of these, the plant-based alkaloid decamethylenediguanide, was discovered in the 1920s. Although it succeeded in reducing blood glucose levels, its use was banned due to its marked hepatotoxic effect. In 1955, a sulfonylurea compound named carbutamide was introduced and it was followed by less toxic variants (5, 6). Patients who benefit the most from oral antidiabetic medications are those with a diabetes onset age above 40 years and a diabetes duration less than 5 years.

Patients with longer diabetes duration may need to take insulin and oral antidiabetic medications in combination to keep blood glucose levels under control (7). Oral antidiabetic agents that regulate blood glucose are known to take effect by increasing insulin secretion, elevating insulin sensitivity, or decreasing carbohydrate absorption. An ideal antidiabetic agent should reduce plasma glucose values to the normal range, have minimal side effects, and also inhibit the development of microvascular complications. Glycemic targets can be reached by considering the advantages and disadvantages of these medications and administering them alone or in combination accordingly (8). Currently, metformin is the only biguanide medication in use. At the cellular level, metformin takes effect by indirectly activating AMPK (5'-adenosine monophosphate-activated protein kinase) and partially inhibiting mGPD (glycerophosphate dehydrogenase). Metformin inhibits the elevated glucogenesis in the liver seen in type 2 diabetes, and suppresses lipid and cholesterol biosynthesis through transient inhibition of the mitochondrial respiratory chain complex I. On the other hand, conventional information suggesting that it slightly increases muscle glucose uptake and fatty-acid oxidation is controversial. Metformin also reduces intestinal glucose absorption, increases insulin sensitivity, and partially suppresses appetite (probably due to its side effects on digestion and perhaps due to its effects that promote GLP-1). As it has been in use for a long time and has a low cost, there is extensive clinical experience on metformin therapy. Its advantages include a low hypoglycemia risk and being neutral for weight gain or having a slight weight-reduction effect (9).Gliclazide, which is a second generation sulfonylurea, increases insulin secretion independently from glucose by blocking the ATP-dependent K channels on the plasma membrane of beta cells respectively for long and short durations. As they have been in use for a long time and have a low cost, there is extensive clinical experience on sulfonylureas. Sulfonylureas were shown to decrease the risk of microvascular complications (9). Meanwhile, although it was proposed that they disrupt the ischaemic preconditioning mechanisms of myocardial cells, these concerns were not corroborated by clinical experience. The effects of sulfonylureas currently in use are relatively short-term and more stable. However, their effectiveness does not last very long (9).

If diabetes is not managed properly, it may create a risk for various complications such as diabetic nephropathy, diabetic neuropathy, coronary artery disease, strokes, leg amputations, and even early death (10). Delaying the progression of diabetes would also benefit national economy by increasing the wellbeing of the population and patients and decreasing the economic load on the health system (11). Optimal glycemic control may prevent potential diabetes-related complications. The importance of glycemic control in diabetic patients is known quite well. Various studies have reported a significant decrease in the incidence of diabetes-related complications, however, these targets are often not met (12, 13). Diabetes is also known as a self-managed disease because most of the care is provided by the patients themselves; therefore, patients are expected to show the required dedication to their self-care in their

daily lives (14). Self-care activities of diabetic individuals include maintaining a healthy diet and physical activity, self-monitoring of blood glucose levels, and taking medications regularly. Daily self-care activities play a critical role in achieving positive health outcomes in diabetes. Many studies have reported a clinically significant relationship between glycemic control and self-care activities (15-20). As stated in the Da Qing Diabetes Prevention Study, diabetes can be prevented or delayed by making drastic changes in the lifestyles of individuals with a high diabetes risk. According to the data presented by the Da Qing Diabetes Prevention Study, following a 6-year lifestyle intervention, diet, exercise, and diet+exercise groups showed a decrease in the incidence of diabetes by 31%, 46%, and 42%, respectively (21). These benefits were shown to last for more than 20 years after the end of the lifestyle intervention (22).

Materials and Methods

Having the aim of evaluating patients diagnosed with type 2 DM who use different oral antidiabetic medications with regard to glycemic control and diabetic complications, this study was conducted after obtaining an ethics committee approval from the Firat University Scientific Research Projects Coordination Unit (Approval date: 19/07/2018, Approval number: 07).

The study group consisted of 200 individuals with Type 2 Diabetes, of which 131 were metformin and 69 were metformin+gliclazide prescribed patient, who presented to the Internal Medicine polyclinic and clinic at Firat University Medical Faculty Hospital between January 2018 and July 2018. Patient data were acquired by a retrospective scan of patient files. Diabetic patients with urinalysis results indicating + proteinuria and/or creatinine>1.2 mg/dl were considered to have diabetic nephropathy. Patients who had been diagnosed with diabetic retinopathy by the Ophthalmology Department after a consultation were included in the retinopathy group. Patients with positive polyneuropathy results in EMG or neuropathic complaints were clinically considered to have diabetic neuropathy. Patients diagnosed with hyperlipidemia and/or cardiovascular diseases after the diagnosis of diabetes were considered in the atherosclerotic cardiovascular diseases category. According to the Wagner grading system for diabetic foot ulcers; patients with superficial ulcers, deep and penetrating ulcers, osteomyelitis, local gangrene or diffuse gangrene were considered diabetic foot patients. Diabetic patients with a blood pressure>130/80 mmHg were considered hypertensive diabetics. Atherosclerosis and diabetic foot patients were included in the 'Type 2 Diabetes with macrovascular complications' group, while patients with nephropathy, retinopathy, and neuropathy were included in the microvascular complications group.

Demographic data of the entire study group (age, sex, waist and hip circumference measurements, body mass index values) were obtained from the scan of patient files. Body mass index measurements were in units of kg/height (m²); obtained by the division of body weight in kilograms to body surface area in units of m². Waist and hip

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circumference measurements were taken using a measure (cm) in accordance with the WHO waist circumference measurement guidelines; making measurements at the midpoint between the costal margin and spina iliaca. Routine biochemistry samples of the patients were evaluated by the central biochemistry laboratory at our hospital and these were comprised of the routine tests requested during follow-up examinations (HbA1c, AST, ALT, Urea, Creatinine, Lipid levels). No additional blood samples were obtained for this study besides those collected routinely and only data recorded in the patient files were used.

Statistical Analysis

Obtained results were evaluated using the SPSS-22 computer software. Categorical data were analyzed with the Chi-square test, parametric data were analyzed with Student's t-test. $p < 0.05$ was considered the threshold for statistical significance.

Results

This study included 200 patients, 131 of which were on metformin monotherapy and 69 on metformin and gliclazide combination therapy. Patients who used only metformin demonstrated an HbA1c value of 7,6%±1,5, while patients who used metformin+gliclazide demonstrated an HbA1c value of 8,2%±1,9. Fasting blood glucose (FBG) and postprandial blood glucose (PBG) levels of the metformin group were respectively determined as 172±50mg/dl and 253±68mg/dl. FBG and PBG levels of the group that underwent metformin and gliclazide therapy were found as 190±61mg/dl and 276±73 mg/dl, respectively. There was a statistically significant difference between the two groups with regard to these values ($p < 0.05$). Body mass index (BMI) values were determined as 28,2±5.5 for the metformin group and as 28,6±5,4 for the metformin+gliclazide group (Table 1).

With regard to microvascular complications, the two groups did not demonstrate any statistically significant differences. However, we found that diabetic peripheral neuropathy was quantitatively more common among patients on metformin monotherapy compared to the metformin+gliclazide group (61 versus 41 patients) (Table 2).

Table1: Comparison of Laboratory Parameters of Metformin Therapy Group and Metformin + Glyclazide Therapy Group

Parameters	Metformin Group (n=131)	Metformin+gliklazid Group (n=69)	P Value
Age	55,26±8,717	57,01±8,702	0,17
HbA1c (%)	7,605±1,5258	8,296±1,9615	0,006*
FBG (mg/dl)	172,98±50,483	190,78±61,681	0,029*
PBG (mg/dl)	253,36±68,452	276,29±73,872	0,030*
BMI	28,28±5,539	28,61±5,443	0,691
LDL-C (mg/dl)	125,20±46,758	126,46±42,838	0,85
Creatinin (mg/dl)	0,7356±0,13635	0,7325±0,17039	0,889

* Statistically significant differences. BG; Blood Glocose FBG (Fasting blood glucose); PBG (Postprandial blood glucose); BMI (Body mass index)

Table2: Comparison of the group receiving metformin treatment and the group receiving metformin + glyclazide treatment in terms of microvascular complications

		Nephropathy		
		yes	no	Total/p value
Group	metformin	1	130	131/0.2
	metformin+gliclazid	2	67	69/0.5
Total		3	197	200
		Neuropathy		
		yes	no	Total/p value
Group	metformin	61	70	131/0.84
	metformin+gliclazid	41	28	69/0.11
Total		102	98	200
		Retinopathy		
		yes	no	Total/p value
Group	metformin	26	105	131/0.14
	metformin+gliclazid	20	49	69/0.19
Total		46	154	200

Discussion

Type 2 diabetes mellitus (T2DM) is a chronic disease that can result in serious comorbid conditions, as well as a high rate of mortality (4). If metabolic parameters (fasting blood glucose, postprandial blood glucose, hemoglobin, A1c, blood pressure, lipids) are not monitored effectively in diabetes, various complications such as diabetic nephropathy, diabetic neuropathy, coronary artery disease, stroke, leg amputations due to diabetic foot infections, and even an early death may become a risk (10). The prevention of these complications would also benefit national economy by increasing the patients' quality of life and decreasing the associated economic load on the health system (11).

Optimal glycemic control may prevent potential diabetes-related complications. Although the importance of glycemic control in diabetic patients is clear, various studies have reported a significant decrease in the incidence of diabetes-related complications that is often not achieved in clinical practice (12,13). Diabetes is also known as a self-managed disease because most of the care is provided by the patients themselves; therefore, patients are expected to show the required dedication to their self-care in their daily lives (15).

Personal care activities of diabetic individuals include maintaining a healthy diet and physical activity, self-monitoring of blood glucose levels, and regular use of medication. Daily self-care activities play a critical role in achieving positive health outcomes in diabetes. Many studies have reported a clinically significant relationship between glycemic control and self-care activities (15-20).

In this study, we evaluated and compared patients diagnosed with Type 2 DM who were on different oral antidiabetic agents in terms of glycemic control and diabetic complications. This study included 200 patients, 131 of which were on metformin monotherapy and 69 on metformin and gliclazide combined therapy. Patients who used only metformin demonstrated an HbA1c value of 7,6%±1,5, while patients who used metformin+gliclazide demonstrated an HbA1c value of 8,2%±1,9. Here, the reason for the lower HbA1c values seen in patients on metformin monotherapy may be that baseline glycemic values were lower in this group and that patient adherence to monotherapy was higher. Fasting blood glucose (FBG) and postprandial blood glucose (PBG) levels of the metformin group were respectively determined as 172±50mg/dl and 253±68mg/dl. FBG and PBG levels of the group that underwent metformin and gliclazide therapy were found as 190±61mg/dl and 276±73 mg/dl, respectively. There was a statistically significant difference between the two groups with regard to the present values (p<0.05).

Here, it can be stated that the group on metformin+gliclazide is quite far from the glycemic goals in terms of fasting and postprandial blood glucose levels and that a different oral antidiabetic medication or insulin should be considered as alternatives. With regard to microvascular complications, the two groups did not demonstrate any statistically significant differences. The most important conditions for the appearance of

microvascular complications are diabetes duration and fluctuating glycemic values throughout this duration, thus, our inability to acquire diabetes duration data from patient files due to the retrospective nature of our study constitutes one of the important limitations of this study. Body mass index (BMI) values were determined as 28,2±5.5 for the metformin group and as 28,6±5,4 for the metformin+gliclazide group.

While there was not a statistically significant difference, the higher BMI values seen in patients using metformin+gliclazide can partially explain the higher glycemic values determined in this group. Another issue that is worth stressing here is that both groups had high BMI values, highlighting the importance of selecting antidiabetic agents that facilitate weight loss while evaluating treatment options and making lifestyle changes, particularly concerning dietary habits.

Glycemic targets must certainly be individualized. More flexible glycemic targets must be set in cases of low life expectancy, long diabetes duration, recurrent episodes of severe hypoglycemia, concomitant micro and macrovascular complications or other comorbid conditions.

In the case that glycemic control is not maintained in patients undergoing one of the current non-insulin antihyperglycemic therapies, individualized treatment alternatives and therapies in combination with insulin would be more appropriate. It is recommended that patients with type 2 diabetes mellitus are introduced to insulin therapy in situations such as type 1 diabetes mellitus, LADA and failed metabolic control with non-insulin antihyperglycemic medications, excess weight loss, severe hyperglycemic symptoms, hyperglycemic emergencies, acute myocardial infarction, inflammatory and systemic diseases, major surgery, pregnancy and lactation, severe liver and kidney failure, allergy to or strong side effects by non-insulin antihyperglycemic medications, clinically severe insulin resistance, and long-term high-dose corticosteroid use (23).

(Type 2 diabetes, commonly resulting from lifestyle and diet, thus has very close relation with lifestyle, this relation should be emphasized strongly) It is known that having adequate information as to type 2 DM and managing diabetes with a correct approach increase compliance with treatment and play an important role in the management of diabetes (24). Knowledge on type 2 DM and knowledge and awareness about correct nutrition help individuals with type 2 diabetes establish metabolic self-control and make dietary choices that would optimize quality of life (25). In overweight or obese adults with type 2 DM, weight loss attempts that depend on lifestyle interventions result in less than 5% weight loss and weight loss targets are often not achieved (26).

In cases where more than 5% weight loss is achieved through lifestyle changes, studies report favorable effects on glycemic levels, blood pressure, and the lipid profile (26). In order to be able to achieve such levels of weight loss, intensive interventions including energy restriction, regular physical activity, and regular follow-up visits to health professionals were reported to be necessary. A study

done by Franz et al. (26) expressed that weight loss was not a realistic primary treatment strategy for most individuals with a diagnosis of type 2 DM and a high body mass index. However, they propose that nutritional therapy promotes a healthy diet and that reduced energy intake, regular physical exercise, and education reinforce the primary treatment strategies.

On the other hand, due to low dietary compliance by individuals diagnosed with Type 2 DM, a well-balanced, simple, and easily understandable dietary approach is recommended (27).

In conclusion; the findings of our study that indicate suboptimal glycemic control may be explained by the incorrect dietary habits of the patients, lack of sufficient exercise and walking, poor compliance with the medical treatment proposed by the physician, and mentally, lack of awareness regarding the severity of the disease.

Our opinion is that the desired states in diabetes management can be reached by maximum patient compliance with the lifestyle changes proposed for their disease, providing environments that facilitate patient education, and multidisciplinary teamwork by physicians, nurses, dieticians, psychologists, and other allied health professionals.

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