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Type 2 Diabetes Patients on Dual Oral Therapy: Does Glycemic Control Continue to Deteriorate in these Patients?

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ABSTRACT

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Objectives: The objective of this retrospective analysis was to evaluate the glycemic control and cardiac parameters in patients with type 2 diabetes mellitus who were prescribed dual oral therapy after the failure of diet, exercise and metformin monotherapy.

Methods: Type 2 diabetics patients who were added a second oral agent to the previous metformin monotherapy at least 3 months prior to the baseline visit were followed during June 2012 to June 2013. Data collected from the patient files included demographic characteristics, medical history, physical examination findings, diabetes related laboratory measurements and treatment recommendations in each visit. The patients were followed up in a scheduled manner every three months and the above data were recorded in each visit.

Results: A total of 61 patients with a mean age of 54.8±10.7 years participated in the study. During the study, HbA1c declined in the first visit and then started to increase gradually. Only 32.8% of patients achieved HbA1c ⩽ 7%. The fasting blood sugar escalated gradually from the baseline to the fourth visit and only 13.1% of patients achieved ⩽ 110 mg/dl. There was no marked change in the blood pressure, body weight and BMI. There was insignificant reduction in the total cholesterol and triglyceride level and there was no marked change in LDL, HDL and VLDL.

Conclusion: Our findings suggest that the progressive deterioration of HbA1c observed while patients were treated with dual oral therapy and highlights the importance of aggressive monitoring and prompt intervention to improve glycemic control in type 2 diabetes patients

Keywords: BMI, Body Weight, Fasting Blood Sugar, Glycemic Control, HbA1c, Type 2 diabetes mellitus.

INTRODUCTION

Type 2 diabetes mellitus is a chronic progressive metabolic disorder associated with significantly increased risk of cardiovascular morbidity and mortality. Type 2 diabetes mellitus accounts for about 90% of all cases of diabetes[1] and is rapidly becoming a major health issue globally with an estimated 5% of the world population affected in 2005. Diabetes represents a growing worldwide epidemic and is a major global health and economic concern. Evidence has indicated that both the prevalence and incidence of diabetes are on the rise, with both increasing by approximately 5% annually in the US over the past 15 years.[2,3]

The natural history of T2DM typically involves progressive pancreatic islet cell dysfunction and worsening glycemic control. Type 2 diabetes is physiologically characterized by progressive beta-cell dysfunction in the setting of relatively fixed insulin resistance. 90% of type 2 diabetics are insulin resistant, but the degree of insulin resistance is nearly maximal by the time patients reach IGT.[4]

The degree of relative beta-cell dysfunction in early diabetes has long been appreciated, with absolute hyperinsulinemia common at diagnosis but still relative insulin deficiency in that blood glucose remains elevated. However, data from the UK Prospective Diabetes Study (UKPDS) and more recently from the San Antonio Metabolism study[5] have suggested that absolute beta-cell function has declined 50% in early IGT and that at diagnosis, as much as 80% of beta-cell function may have been lost. This suggests a more advanced disease state than is clinically apparent from glycemia, making current treatment paradigms somewhat discordant from disease state. Additionally, UKPDS 16 offered the insight that loss of beta-cell function is an intrinsic and progressive part of the disease process of diabetes and was not therapeutically well-addressed over the course of the study with monotherapeutic metformin, sulfonylurea or insulin therapy.

The American Diabetes Association (ADA) recommends lifestyle modifications for initial pharmacological therapy of type 2 diabetes mellitus.[6] When lifestyle modification alone can no longer maintain desired glycemic targets and clinicians and patients decide to begin drug therapy,

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sulfonylurea (SU) or metformin monotherapy are typically the first-line agents of choice.[7] Adding a sulfonylurea or insulin when metformin monotherapy is insufficient to reach or maintain target goals. The thiazolidinedione pioglitazone may be recommended when the risk of hypoglycemia is especially undesirable, and the glucagon-like peptide- 1 (GLP-1) analog exenatide may be recommended if weight loss is a major goal of therapy. [6]

Among these, sulfonylurea and metformin are frequently used in combination after monotherapy fails, but the success of sulfonylurea/metformin combination therapy (SU/MET) is often short-lived,[8] with HbA1c escalation resuming as early as 6 months after SUs are added to metformin. [9]

With recent evidence indicating the potential benefit of more aggressive, stepwise therapy in type 2 diabetes, a number of algorithms have been published to facilitate timely treatment transitions in response to persistently elevated glucose levels. [10,11,12]

HbA1c is currently the standard serum marker applied to assess overall glycemic control in patients with diabetes. Although national guidelines agree that targeting an HbA1c level of < 7% or even lower is desirable for the majority of patients[13, 14] HbA1c control remains elusive for most patients. Results from one national survey conducted in 2004 revealed that 73% of individuals with type 2 diabetes had HbA1c levels that exceeded target .[15]

The present study was aimed to determine the the glycemic control and cardiac parameters in patients with type 2 diabetes mellitus who were prescribed dual oral therapy after the failure of diet, exercise and metformin monotherapy.

MATERIALS AND METHODS

This was a single-centre, retrospective study conducted at Asir Diabetes Center, Abha, K.S.A from June 2012 to June 2013 in accordance with Good Clinical Practice, evaluating the effect of dual oral drug therapy in type 2 diabetes patients in whom glycemic targets were not achieved with the use of single oral hypoglycemic agent. The study protocol was reviewed and approved by the Institutional Review Board.

A sum of 61 patients with type 2 diabetes who were added a second oral agent to the previous metformin monotherapy at least 3 months prior to the baseline visit were followed during followed for one year.

Patients with T2DM who were inadequately controlled while receiving single oral hypoglycemic agents were recruited in the study after satisfying the following criteria: diagnosis of type 2 diabetes, any one of the oral hypoglycemic agent added to MF monotherapy at least three months prior to the baseline visit and HbA1c >7%.

Exclusion criteria for the study were: Type 1 diabetes, Insulin therapy, malnutrition associated diabetes, drug-induced diabetes, patients with deranged liver function tests, serum creatinine >1.5 mg/dl, pregnancy, drug or alcohol dependence and if he/she was unable to understand the regimen.

Data collected from the patient files included demographic characteristics, medical history, physical examination findings, diabetes related laboratory measurements and treatment recommendations in each visit. The patients were followed up in a scheduled manner every three months and the above data were recorded in each visit.

At the start of treatment, all patients were educated about the proper measurement and recording of blood glucose, awareness and management of hypoglycemia and nutrition. At each visit, the patients were asked about compliance with meal planning, any hypoglycemia and its management and all information gathered was recorded.

Statistical Analysis:

The analysis of HbA1c, fasting and post prandial glucose, body weight and BMI, and the lipid profile was carried out by using graph pad prism 5.01. Comparison between the baseline values with the value of the first, second, third and fourth visit of treatment were made, as well as comparison in between these months was done by applying one way analysis of variance & the Turkeys multiple comparison test. Value of $P<0.001$ were considered significant.

RESULTS

The demographic characteristics of the patients are described in Table 1. The study consisted of 61 patients with a mean age of 54.8±10.7 years. Of these participants, 65.5 % were males and the remaining 34.5 % were females. The mean duration of diabetes was 5.4±5.1 years. Among these participants, majority of the patients (54.1%) had first degree family history of diabetes mellitus followed by the hypertension (18%). 18% of the second degree relatives of the participants had diabetes mellitus.

A range of diabetes related microvascular and macrovascular complications were seen among the patients at the time of enrolment. More patients were affected by dyslipidemia (72.1%) followed by hypertension (45.9%). 9.8% of the patients were affected by neuropathy and 6.6% of patients were affected by the ischemic heart disease. The other diabetes related complications were affecting these patients only minimally as follows: retinopathy (4.9%), impotence (3.3%), depression (3.3%), diabetic foot (1.6%) and cerebrovascular accident (1.6%).

The patients in the age group 51-60 years were affected more (34.4%). Next to this age group, 24.6% of patients in the age between 41- 50 and 61-70 were affected. 9.8% of patients

Table 1: Demographic characteristics of patients on Two OHA:

Parameters	Number	Percentage
N	61	–
Gender (M/F)	40/21	65.5 / 34.5
Age (Mean Years± SD)	54.8±10.7	
Duration of Diabetes (Years)	5.4±5.1	
Age at diagnosis (Mean Years± SD)	49.4 ± 10.1	
Family history		
1st degree		
Nil	14	23
DM	33	54.1
HTN	11	18
IHD	1	1.6
Obesity	2	3.3
2nd degree		
Nil	49	80.3
DM	11	18
HTN	1	1.6
Diabetes related complications		
Hypertension	28	45.9
Dyslipidemia	44	72.1
Neuropathy	6	9.8
Retinopathy	3	4.9
Diabetic foot	1	1.6
Impotence	2	3.3
DKA	0	0
IHD	4	6.6
CVA	1	1.6
Depression	2	3.3

OHA- Oral Hypoglycemic Agent; DM-Diabetes Mellitus; HTN-Hypertension; IHD-Ischemic Heart Disease; DKA-Diabetic Ketoacidosis; CVA- Cardiovascular Aneurism

were found in between 30- 40 years and only 6.6% of patients were found between the age 71-80 years.

The combination of oral hypoglycemic agents in the study subject is given in the table 2. Majority of patients were prescribed with the combination of glibenclamide and metformin (80.3%) followed by Gliclazide + Metformin (11.5%), Glimepride + Metformin (6.6%) and Roziglitazone + Metformin (1.6%).

Glycemic Control:

The change in HbA1c over the 12 months is shown in the table 3. Over the course of the study, HbA1c (Mean ± SD) declined in the first visit and then started to increase gradually from the value of first visit. The change in HbA1c is as follows: At the baseline, the HbA1c was 8.3 ± 2.2%. At the

Table 2: Combination of OHA therapy of the study subjects at the baseline visit:

Combination	Number	%
Glibenclamide + metformin	49	80.3
Gliclazide + Metformin	7	11.5
Glimepride + Metformin	4	6.6
Roziglitazone + Metformin	1	1.6
Total	61	100

first Visit [third month] the HbA1c decreased to 7.58±1.45%. From the second visit, the escalation of the HbA1c value is as follows: (7.59±1.67%), (7.94±1.87%) and (8.22±1.85%) respectively in the second, third and fourth visits. The above HbA1c values on subsequent visits are not significant.

The fasting blood sugar also followed the same pattern. There was no decrement in the FBG, but the escalation was gradual from the baseline to the fourth visit. The changes in the FBG in each visit is as follows (mg/dl ± SD): 139.13 ± 36.43 mg/dl at baseline, 140.89 ± 79.12 mg/dl at the first visit, 139.36 ± 46.90 mg/dl at the second visit, 147.64 ± 59.16 mg/dl at the third visit and 155.07 ± 56.73 mg/dl at the fourth visit.

Of the total 61 patients, only 32.8% of patients achieved HbA1c ⩽ 7%, and only 13.1% of patients achieved the target fasting blood glucose level (⩽ 110 mg/dl).(table 4)

Blood Pressure:

There is no much difference in the systolic and diastolic blood pressure. The blood pressure was nearly normal at the baseline visit (SBP: 122.8 ± 16.44 mmHg and DBP 77.05 ± 8.24 mmHg) and continued to be the same in the subsequent visits as shown in the table 3.

Body weight and BMI:

The body weight and the BMI were controlled well with the 2 OHA. The baseline body weight of the participants was 76.64 ± 13.68 kg and continue with slight changes in the subsequent visits. In the same way, the BMI was also maintained as the baseline (29.87 ± 5.28 kg/m^2) with slight changes in the subsequent visits.

Lipid Profile:

The favorable lipid profile was seen in these patients. The total cholesterol level at the baseline was 185 ± 46.83 mg/dl and decreased gradually in the subsequent visits (172.3 ± 43.71 mg/dl at the fourth visit). The baseline triglyceride was 195.5 ± 154.6 mg/dl. There were fluctuations in the triglyceride levels in the subsequent visits. The level was decreased from the baseline in the first visit and slightly increased in the second and third visits. However, the level was decreased again in the fourth visit. The level of triglyceride in the first, second, third and fourth visits are as

Table 3: Changes in parameters in subsequent visits:

Parameter	BASELINE (mean ± SD)	I visit (mean ± SD)	II visit (mean ± SD)	III visit (mean ± SD)	IV visit (mean ± SD)	P value
Glycemic parametes						
HbA1c(%)	8.30 ± 2.2	7.58±1.45	7.59±1.67	7.94±1.87	8.22±1.85	0.0802
FBG (mg/dl)	139.13±36.43	140.89±79.12	139.36±46.90	147.64±59.16	155.07±56.73	0.4782
Cardiac parameters						
SBP (mmHg)	122.8 ± 16.44	120.7 ± 12.63	120.1 ± 14.22	120.7 ± 13.57	122.9 ± 14.36	0.7301
DBP (mmHg)	77.05± 8.24	76.39± 8.37	76.39± 6.59	74.82± 7.45	77.31± 8.32	0.4445
Anthropometric Parameters						
WEIGHT (kg)	76.64 ± 13.68	77.07 ± 13.43	75.73 ± 15.97	76.95 ± 13.41	76.81 ± 13.22	0.9861
BMI (kg/m^2)	29.87 ±5.28	30.04 ±5.24	29.43 ±6.02	30.00 ± 5.27	29.95 ± 5.21	0.9717
Lipid Profile						
TC (mg/dl)	185± 46.83	181.7± 41.83	175.5± 39.66	175.1± 48.1	172.3± 43.71	0.4910
TGL (mg/dl)	195.5 ± 154.6	164.2 ± 68.25	173.1 ± 110.9	180.4 ± 98.32	169.4 ± 69.63	0.5170
LDL (mg/dl)	112.1 ± 33.54	118.1 ± 57.32	102.7 ± 39.21	107.4 ± 40.93	106.2 ± 36.83	0.3027
HDL (mg/dl)	41.84 ± 11.86	41.18 ± 14.60	41.18 ± 12.74	40.69 ± 13.22	40.67 ± 14.31	0.9892
VLDL (mg/dl)	32.34 ± 16.02	30.30 ± 11.78	30.80 ± 15.34	32.43 ± 11.09	33.07 ±9.87	0.7379

HbA1c- Glycated hemoglobin; FBG- Fasting Blood Glucasoe; SBP- Systolic Blood Pressure; DBP-Diastolic Blood Pressure; BMI- Body Mass Index; TC- Total Cholesterol; TGL- triglyceride; LDL-Low density Lipoprotein; HDL- High Density Lipoprotein; VLDL-Very Low density Lipoprotein

Table 4: Number of patients achieving the glycemic goal at the final visit:

S.No	Parameter	Number	%
1	HbA1c	20	32.8
2	FBG	8	13.1

follows: 164.2 ± 68.25 mg/dl, 173.1 ± 110.9 mg/dl, 180.4 ± 98.32 mg/dl and 169.4 ± 69.63 mg/dl. There was no much difference in the levels of LDL, HDL and VLDL.

DISCUSSION

The ADA recommends drug therapy for treatment of type 2 DM based on the drug's ability to reduce hyperglycemia.[16] If lifestyle intervention and the maximal tolerated dose of metformin fail to achieve or sustain the glycemic goals, another medication should be added within 2–3 months of the initiation of therapy or at any time when the target HbA1c level is not achieved. Another medication may also be necessary if metformin is contraindicated or not tolerated. The consensus regarding the second medication added to metformin was to choose either insulin or a sulfonylurea.[6]

This study evaluated the glycemic control and other cardiovascular parameters such as weight, BMI and lipid profile in metformin-failed patients. These parameters were taken in each visit (every three months) and compared with the baseline.

The glycemic control of the participants was improved in the first visit. The mean HbA1c was reduced from 8.3% (baseline) to 7.58% (first visit). But, the glycemic control was progressively deteriorated in the subsequent visits. The glycemic control kept on deteriorating and approximately 70% of patients were not at goal HbA1c level ($\leqslant$7%) after the addition of sulfonylurea or other oral hypoglycemic agents to their metformin monotherapy at the end of the study. This result is in agreement with the findings of a similar study conducted by Jermendy et al.[16] which evaluated the outcomes of adding second hypoglycemic drug after metformin monotherapy failure among type 2 diabetes patients.

Based on this study, it was found that the progressive deterioration in HbA1c observed while the patients were treated with combination of two oral hypoglycemic agents in which majority of patients had metformin as one of the drug in the combination. This observation is in line with the study conducted by Cook et al [9] which evaluated the impact of combination therapy (metformin and sulfonylurea) on glycemic control.

The median HbA1c rose from 7.58% to 8.22% from the first visit to the fourth visit. This observation is consistent with UKPDS the findings for oral monotherapy among newly diagnosed patients with diabetes.[17]

The weight of the participants in this study was nearly stable throughout the study period. Even though, weight gain is one of the major side effect of the insulin secretagogues, metformin was one of the component of combination in all the

cases. According to Kalra et al study,[18] metformin reduces weight gain, and may cause weight loss, when given alone or in combination with other drugs.

Sulfonylurea use is linked to significant weight gain.[19] Addition of sulfonylureas to metformin is also associated with weight gain, but to a lesser degree, according to meta analysis.[20] A meta-analysis has shown that a combination of sulfonylurea and insulin does not lead to weight gain.[21]

The overall prevalence of hypertension in diabetic patients is greater than 70%, and elevated blood pressure (BP) significantly increases the risk of complications of diabetes. The results of our study regarding the blood pressure showed no much difference in the systolic and diastolic blood pressure. The patients' mean blood pressure remained normal throughout the study period.

Even though the type 2 patients are vulnerable to hypertension, the combination of two oral agents plays an important role in controlling blood pressure. The patients are on combination of two oral agents and having controlled blood pressure. This is consistent with the randomized controlled study conducted by Michel Komajda et al, stating that treatment with different oral hypoglycemic drugs is known to have variable effect on BP. When thiazolidinediones / sulfonylurea combined with metformin were shown to decrease BP.[22]

This results of our study is also in line with the result of a randomized trial (UKPDS 28), which reveals that there is no significant change in the blood pressure in sulfonylurea plus metformin treated patients.[23]

The total cholesterol, triglyceride and low density lipoprotein in the fourth visit were decreased from the baseline visit. The high density lipoprotein was slightly decreased in the fourth visit when comparing to the baseline value. These findings are in agreement with the findings of a meta-analysis of randomized controlled trials conducted by Zhang F et.al [24] who analysed the effects of sulfonylurea plus metformin on lipids, blood pressure, and adverse events in type 2 diabetes.

CONCLUSION

Our data suggest that more than one third of patients had not reached the glycemic goal (HbA1c $\leqslant$ 7%) 1 year after starting dual oral therapy. Many physicians wait several months after patients' first post - metformin plus sulfonylurea HbA1c test result $\geqslant$ 8.0% before prescribing a new agent, with most therapy changes occurring only after HbA1c was well $\geqslant$ 9.0%. Our findings suggest that the progressive deterioration of HbA1c observed while patients are treated with metformin plus sulfonylurea and highlights the importance of aggressive monitoring and prompt intervention to improve glycemic control in patients with type 2 diabetes.

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