Original Article

Are Oral Hypoglycemic Agents Suitable as the First-line Treatment for Newly Diagnosed Type 2 Diabetes in Patients with Severe Hyperglycemia?

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Abstract

Objectives: To investigate if starting oral antihyperglycemic agent was enough to achieve the target glycated hemoglobin (HbA1c) in patients with newly diagnosed type 2 diabetes mellitus (T2DM), despite severe hyperglycemia, with or without symptoms. **Patients and Methods:** This was a retrospective patient data analysis for patients with newly diagnosed T2DM during January to December 2013. At baseline and after 3 months, HbA1c was measured. All patients started a diet and lifestyle changes in addition to oral hypoglycemic agents. **Results:** The enrolled patients were 764 in number. Of them, 331 (42.9%) achieved the target HbA1c <7% by oral hypoglycemic agents after 3 months, regardless of the treatment used. Multivariable logistic regression analysis showed that only presenting fasting plasma glucose <150 mg (odds ratio [OR] 2.193, 95% confidence interval [CI] 1.297–3.709) and drug treatment (OR 1.320, 95% CI 1.100–1.585) were the independent variables associated with achieving the glycemic target. **Conclusions:** Using antihyperglycemic agents as the first line for new T2DM, 42.9% patients can achieve target glycemic control. Even those with gross glycemic abnormalities, more than 60%, can achieve target glycemic control using diet, lifestyle change, and metformin. Prospective trials are needed to confirm such findings.

Keywords: Glycated hemoglobin, oral hypoglycemic agents, type 2 diabetes

Introduction

All the available guidelines recommend metformin as the initial drug of choice in patients who are newly diagnosed with type 2 diabetes mellitus (T2DM) or in whom lifestyle modifications fail to attain glycemic control, unless contraindicated.[1-6] At diagnosis, highly motivated patients with glycated hemoglobin (HbA1c) already near the target (e.g., <7.5%) could be given a chance to engage in a lifestyle change for 3–6 months before starting on the drug (usually metformin).[1] Those patients with moderate hyperglycemia or in whom lifestyle changes are anticipated to be unsuccessful should promptly be commenced on an antihyperglycemic agent (usually metformin) at diagnosis, which can later be modified or possibly discontinued if lifestyle changes are successful.[1]

When to initiate insulin in new patients with T2DM remains unclear among guidelines. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) state that insulin should be used as the first line at diagnosis in patients with significant baseline hyperglycemia with osmotic symptoms of hyperglycemia and plasma glucose >300 mg/dL or HbA1c >10%.[1] This recommendation has remained unchanged by the ADA from 2013 onward.[7,8] On the other hand, the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) recommend starting insulin therapy in symptomatic patients with HbA1c >9%.[2] The National Institute for Clinical Excellence of the UK recommends starting insulin if the HbA1c remains >7.5%, despite other measures.[4] The American College of Physicians has not addressed the starting of insulin.[3] Insulin could be used at diagnosis in individuals with severe hyperglycemia according

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to the Canadian Diabetes Association Clinical Practice Guidelines Expert Committee released in 2013.[5]

In Iraq, there are no national guidelines, but most diabetologists presumably follow the aforementioned ADA standards of medical care in diabetes for each year and the joint ADA/EASD position statement.[1,7,8] The extent to which these guidelines are followed has not been ascertained. The aim of this study was to see if starting oral antihyperglycemic agents was enough to achieve target HbA1c in patients with newly diagnosed T2DM despite severe hyperglycemia with or without symptoms.

Patients and Methods

Design and settings

This study was a retrospective data analysis for patients with newly diagnosed T2DM who attended the Faiha Specialized Diabetes, Endocrine, and Metabolism Center in Basrah (Southern Iraq) between January and December 2013. The Center is a tertiary care center, which receives diabetic patients from Basrah and Southern Iraq referred from primary care setting, hospitals, and private practice. The patients visit the center every 3 months, where blood pressure and weight are measured, and blood is taken for HbA1c and 2 h postprandial glucose or fasting plasma glucose (FPG) according to the fasting state. All these measures are repeated for each patient every 3–4 months. Real-time continuous glucose monitoring was feasible in our center. The Ethical Committee of the Basrah Medical College approved the study.

Study population

Patients enrolled had new-onset type 2 diabetes, according to the ADA diagnostic criteria.[7] All patients were started on a diet, lifestyle changes (with the advice given by a treating physician), metformin (generic 1000 mg twice daily after gradually building up the dose over two weeks), and sulfonylurea (usually glimepiride 4 mg daily) or sitagliptin 100 mg daily which was used in the minority. Because of insulin phobia and psychological resistance to insulin among patients with T2DM, most of our patients refused to take insulin regardless of the presenting glycemic level or the HbA1c. All newly diagnosed T2DM seen during the study period were included. Patients with type 1 diabetes, pregnant women, those currently using corticosteroid or in the preceding 1 month, those who left follow-up after 3 months, and those who were started on insulin with or without oral antihyperglycemic drugs were excluded. The treatment was decided by the treating physician based on the clinical needs of the individual patients.

Outcome measures

The database included major demographic features, body mass index (BMI), hypertension, and smoking status. BMI was calculated as the weight (kg)/height^2 (m). Hypertension was defined as either mean of two systolic blood pressure readings ≥140 mmHg or mean of two diastolic blood pressure readings ≥90 mmHg, recorded on the same day, or currently on antihypertensive medication. Smokers were defined as those who have smoked >100 cigarettes at any time and were currently smoking every day or some days.[9] The HbA1c was measured by ion-exchange high-performance liquid chromatography using a D10 Hemoglobin Testing System (Bio-Rad D10; Bio-Rad, Berkeley, CA, USA). Target HbA1c of <7% used in this study was according to the ADA standards of care. Severe hyperglycemia was defined as HbA1c >10% and plasma glucose >300 mg/dl with or without symptoms.[1]

Statistical analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences software version 15.0 (SPSS Inc, Chicago, IL). Continuous variables were summarized as mean ± standard deviation and dichotomous variables as number and percentage. Logistic regression analysis was used to study variables associated with achievement of the glycemic target. A $P < 0.05$ was considered statistically significant.

Results

Patients and management

A total of 764 patients were included in the analysis; 50.4% were women [Table 1]. Their mean BMI was 29.5 ± 7.6 kg/m^2. There were 18.7% current smokers, and 25.8% had hypertension. The mean presenting HbA1c was 9.5% ±2.0%, and 287 (37.6%) had an HbA1c >10% at presentation. The treatment strategy was diet and lifestyle change in 3.1%; diet and lifestyle change with metformin in 64.5%; diet and lifestyle change, metformin, and sulfonylurea in 27.1%; diet and lifestyle change and sulfonylurea in 3.7%; diet and lifestyle change, metformin, and sitagliptin in 1.4%; and diet and lifestyle change, metformin, sulfonylurea, and sitagliptin in 0.1%. Only one patient could not tolerate metformin because of diarrhea and abdominal pain despite gradual dose titration.

Glycemic control

The mean HbA1c reduction in the diet, lifestyle, and metformin treatment group was 2.1 ± 2.4 [Table 2]. We had only one patient treated with diet, lifestyle change, metformin, sulfonylurea, and sitagliptin, whose HbA1c increased by 2.3% by 3 months. Of 764 patients, 331 (42.9%) achieved the target HbA1c <7% by oral antihyperglycemic agents after 3 months [Table 2], regardless of the treatment used (single agent or combination).

Predictors of glycemic control

Of 764 patients, 287 (37.5% patients presented with severe high HbA1c (>10%) and/or 262 (34.2%) patients presented with plasma glucose (>300 mg/dl). Of these, using diet and lifestyle alone, only 0.7% and 1.5% of them achieved the target, respectively, and in those on a diet and lifestyle change and metformin, this was seen in 60.3% and 65.6%, respectively [Table 2]. Multivariable logistic regression analysis showed that only presenting FPG <150 mg (odds ratio [OR] 2.193, 95% confidence interval [CI] 1.297–3.709) and drug treatment (OR 1.320, 95% CI 1.100–1.585) were the

independent variables associated with achieving the glycemic target [Table 3].

Discussion

The main results of this study showed that those patients with newly diagnosed T2DM and with gross hyperglycemia with or without symptoms are amenable for a 3-month trial for of diet, lifestyle change, and oral antihyperglycemic agent if they refuse insulin. For us, the study sample was sufficient to conclude. However, how do we sustain this beneficial effect? This will need another prospective study.

Individualization of strategies and HbA1c targets can easily be done through the position statement suggested by the ADA/EASD experts in 2012.[1] Although this makes sense with regard to improving the glycemic control, it is a challenge to convince our patients of doing that. A stepwise approach to managing glycemia in T2DM was suggested which involves lifestyle, plus oral antihyperglycemic agents as monotherapy or in combination, for all new cases.[10,11] All of the available antihyperglycemic agents, when added to metformin, add some benefit with varying safety profiles.[12] Only 3.1% of patients in our study relied on lifestyle change and diet alone, and more than 96% were using drug treatment which seems to be good if we compare it with a large UK cohort where only half of the patients started oral antihyperglycemic agents along with lifestyle and diet.[13] This is even better than another study in Dutch patients, where 75% started some oral antihyperglycemic agents within 2 years of diagnosis of T2DM.[14] Less than 60% of this study cohort could not achieve the glycemic target. This is similar to that seen in Jordanian patients with T2DM.[15]

Table 1: Baseline characteristics

Variables	Results
Age (years)	52.9±12.3
Gender (men/women), *n* (%)	379 (49.6)/385 (50.4)
BMI (kg/m^2)	29.5±7.6
Smokers, *n* (%)	143 (18.7)
Hypertension, *n* (%)	197 (25.8)
HbA1c on presentation (mean±SD)	9.5±2.0
HbA1c >10%, *n* (%)	287 (37.6)
HbA1c after first 3 months (mean±SD)	7.6±1.8
Fasting plasma glucose, mg/dl (mean±SD)	168.8±70.5
2 h postprandial plasma glucose, mg/dl (mean±SD)	202.4±87.7
2 h postprandial plasma glucose >300 mg/dl, *n* (%)	262 (34.3)

BMI: Body mass index, HbA1c: Glycated hemoglobin, SD: Standard deviation

Despite the high presenting glucose level in this study, target glycemic control was achieved in >60% of patients by 3 months using diet and lifestyle changes along with metformin in those with severe hyperglycemia (HbA1c >10 and/or plasma glucose >300 mg/dl). Most often, these patients had been hyperglycemic for weeks or months before presenting with the usual symptoms of polyuria and polydipsia. During this time, the pancreatic beta-cells are desensitized to glucose-stimulated insulin secretion due to the persistently high ambient glucose concentrations, resulting in insufficient insulin production and availability.[16] Since metformin has no known effect on the beta-cells, it seems prudent to use it as a first-line agent.

The major benefits of metformin are that it usually does not lead to hypoglycemia when used as monotherapy, it is neutral regarding weight loss, and it has been shown to decrease the plasma triglyceride concentration by 10%–20%.[17]

This study also highlighted the obstacles in diabetes care in a developing country like Iraq. Similar constraints that

Table 2: Management, glycated hemoglobin on presentation and after 3 months of treatment for the group as a whole and also grouped by achieving glycated hemoglobin <7 and by their basal glycemic control (measured by glycated hemoglobin and by fasting blood glucose)

Management approach (sole or in combinations)	Baseline data		Outcome for all patients				Outcome for grossly poorly controlled patients	
	n (%)	HbA1c* on presentation	HbA1c percentage after 3 months*	Change on the HbA1c scale	Achieved HbA1c <7%*	Not achieved target HbA1c	Presenting HbA1c >10%*, *n* (%)	Plasma glucose >300 mg/dl*, *n* (%)
Diet and lifestyle alone	24 (3.1)	7.4±1.3	6.4±0.8	−0.9±1.3	17 (70.8)	7 (29.2)	2 (0.7)	4 (1.5)
Diet, lifestyle and metformin	493 (64.5)	9.4±2.0	7.3±1.5	−2.1±2.4	238 (48.3)	255 (51.7)	173 (60.3)	172 (65.6)
Diet, lifestyle, metformin and sulfonylurea	207 (27.1)	10.1±1.9	8.5±2.2	−1.6±2.7	60 (29.0)	147 (71.0)	99 (34.5)	79 (30.2)
Diet, lifestyle, metformin, sulfonylurea, and sitagliptin	1 (0.1)	9.7	12	+2.3	-	1 (100)	None	None
Diet, lifestyle, metformin, and sitagliptin	11 (1.4)	10.0±1.6	7.8±2.0	−1.8±2.9	3 (27.3)	8 (72.7)	5 (1.7)	1 (0.4)
Diet, lifestyle and sulfonylurea	28 (3.7)	9.6±2.0	7.6±1.8	−1.8±3.1	10 (35.7)	18 (64.3)	8 (2.8)	6 (2.3)
Total	764	-	-	-	328	436	287	262

**P* value between groups <0.0001. HbA1c: Glycated hemoglobin

Table 3: Multivariable logistic regression to determine the confounders for achieving glycemic target

Variables	OR	95% CI	*P*
Age <50 years	0.754	0.555-1.024	0.071
Male gender	1.058	0.784-1.427	0.712
BMI <25 kg/m^2	0.938	0.784-1.427	0.710
Presenting HbA1c <8%	1.498	1.044-2.151	0.028
Fasting plasma glucose <150 mg/dl	2.193	1.297-3.709	0.003
2 h postprandial glucose <200 mg/dl	1.577	1.141-2.179	0.006
Drug treatment	1.320	1.100-1.585	0.003

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, HbA1c: Glycated hemoglobin

affect optimal diabetes care due to various factors, including the inadequate health-care system, lack of financial and professional human resources, insufficient laboratory support, and limited availability of medications were also reported in Oman.[18]

The major limitation of this study is its retrospective cohort design. Because of different presenting glycemic levels of the study participants, it seems logical that those with mild hyperglycemia will gain benefit from diet and lifestyle change with metformin more than those with gross hyperglycemia.

Conclusions

The use of oral hypoglycemic agents as the first line for new T2DM patients can achieve the target glycemic control in 42.9% of all patients. In those with severe hyperglycemia, more than 60% can reach target glycemic control using diet, lifestyle modification, and metformin. Prospective trials are needed to confirm these findings.

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Authors' contribution

All authors participated in the study design, data collection, and analysis, interpretation of the results, and drafting and approval of the final version.

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Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

The study was approved by the Ethical Committee of the Basrah Medical College, Basrah, Iraq. No consent is possible in retrospective chart survey exercises.

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