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Observational Study of Patients in Morocco With Uncontrolled Type 2 Diabetes Treated With Metformin and/or Sulfonylurea With or Without Insulin

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Abstract

Background: Several types of oral antidiabetic drugs (OADs), with or without insulin, may be used to achieve glycemic control in patients with type 2 diabetes mellitus (T2DM). However, real-life studies assessing diabetes treatments in Morocco are rare. Our aim was to assess the efficacy of various antidiabetic treatment regimens to achieve glycemic control in patients with uncontrolled T2DM, to determine the factors associated with a lack of glycemic control and to compare the clinical outcome after 26 weeks of treatment in a real-life setting.

Methods: This prospective, observational study was carried out on 1,377 patients with uncontrolled T2DM in 139 Moroccan centers. Three groups of patients were defined according to the type of treatment: group 1: metformin and/or sulfonylurea only; group 2: metformin and/or sulfonylurea + insulin prior to inclusion; and group 3: metformin and/or sulfonylurea + started on insulin at or after inclusion. Clinical data including glycated hemoglobin (HbA1c), fasting blood glucose (FBG), blood pressure and weight were recorded at inclusion and after 3 and 6 months of treatment.

Results: Mean HbA1c decreased from 9.7±1.8% at baseline to 7.5±1.2% at week-26 follow-up ($P < 0.001$) and the proportion of patients with controlled glycemia (HbA1c < 7%) increased from 10.8% at 12 weeks to 32.4% after 26 weeks of treatment ($P < 0.001$). Mean decreases in HbA1c at 26 weeks were: -1.8% in group 1 ($P < 0.001$), -2.7% in group 2 ($P < 0.001$) and -2.1% in group 3 ($P < 0.001$). Lack of glycemic control was related to non-observance of lifestyle recommendations, lack of treatment efficacy, poor treatment compliance and absence of diabetes education. Uncontrolled glycemia was significantly associated with obesity, hypertension, dyslipidemia, use of one OAD only and no insulin therapy. Mean weight of all patients decreased over the 26-week period, irrespective of treatment regimen.

Conclusion: In a Moroccan primary care setting, observed treatment of T2DM with lifestyle recommendation, metformin, sulfolylurea and insulin was associated with improvement of glycemic control without weight gain.

Keywords: Glycemic control; Observational study; Metformin; Sulfonylurea; Type 2 diabetes mellitus; Insulin

Introduction

Patients with type 2 diabetes mellitus (T2DM) require pharmacological intervention to control their blood sugar levels. However, therapy adjustment is often necessary over time due to disease progression [1]. Measurement of glycated hemoglobin (HbA1c) is an indicator of the status of glycemic control over the previous 3 months. Maintaining an HbA1c level of < 7% is important for the prevention of the micro- and macrovascular complications of diabetes [1-4].

Recent reports from the USA estimate that about one half (48.7%) of patients with T2DM do not meet the glycemic targets and only 14.3% meet the targets for the three measures recommended by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), namely glycemic control (HbA1c < 7%), blood pressure <130/80 mm Hg and low density lipoprotein cholesterol < 100 mg/dL [5]. In Morocco, the IDMPS study claimed that only 30.9% of patients with T2DM achieved the target HbA1c of < 7% and only 0.4% attained all three recommended targets [6].

Management of T2DM includes multiple oral antidiabetic drug (OAD) agents, particularly metformin and sulfonylurea, with insulin only used as a final resort when oral treatments are ineffective, because insulin can lead to weight gain and hypoglycemia [7-9].

The aims of this prospective, non-interventional, real-life study were: 1) to investigate the extent of glycemic control, as measured by HbA1c, in patients with T2DM treated with metformin and/or sulfonylurea with or without insulin in routine daily practice in Morocco; 2) to determine the factors associ-

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Table 1. Socio-Demographic and Clinical Characteristics of the Study Population by Diabetes Treatment at Inclusion

Characteristics	Met and/or Sulf (n = 910)	Met and/or Sulf + insulin (n = 467)	P*
Male, n (%)	413 (45.7)	175 (37.9)	0.006
Age at inclusion (years)	56.0 ± 9.9	57.9 ± 10.1	0.001
Diabetes duration (years)	6.8 ± 5.3	10.2 ± 5.6	< 0.001
Weight (kg)	77.7 ± 12.2	76.8 ± 12.3	0.201
Waist measurement (cm)	98.5 ± 13.5	96.5 ± 15.2	0.024
BMI (kg/m^2)	28.3 ± 4.4	28.4 ± 5.3	0.677
Blood pressure (mm Hg)			
Systolic	141.2 ± 20.4	147.0 ± 22.9	< 0.001
Diastolic	82.0 ± 11.9	83.8 ± 11.6	0.007
Clinical history			
Previous cardiovascular disease†	52 (5.8)	69 (15.2)	< 0.001
Microvascular disease‡	218 (24.2)	210 (46.1)	< 0.001
Laboratory data			
HbA1c (%)	9.3±1.7	10.3±1.9	< 0.001
FBG (mg/dL)	233.9 ± 71.0	269.8 ± 80.8	< 0.001

Continuous data are presented as mean (± SD) and categorical data are shown as n (%). BMI: body mass index; FBG: fasting blood glucose; Met: metformin; Sulf: sulfonylurea. *P values were calculated using the Chi-square test for categorical variables and Student's *t*-test for continuous variables. †Previous cardiovascular disease comprises angina, myocardial infarction, heart failure, stroke and peripheral vascular disease. ‡Microvascular disease comprises retinopathy, neuropathy or nephropathy.

ated with a lack of glycemic control; and 3) to compare the clinical outcomes of these patients after 26 weeks of treatment.

Materials and Methods

Study design

This prospective, observational, multicenter, national epidemiological study was carried out between May 2011 and July 2012. A total of 150 centers (general practitioners) across Morocco were asked to participate. Adult patients with T2DM were enrolled. Inclusion criteria included: age > 18 years; uncontrolled T2DM (HbA1c > 7%) previously treated with one OAD (sulfonylurea or metformin) or two OADs (free combination of sulfonylurea and metformin); ability to undergo an HbA1c test. Patients were excluded if they were pregnant or had type 1 diabetes mellitus. All patients made three visits to the centers: an inclusion visit and two follow-up visits 2 - 3 months apart. Thus, the follow-up period for each patient was 26 weeks.

The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines and was approved by local ethics committees. All study participants gave their written informed consent.

Estimated sample size

For an expected decrease in HbA1c of 1% (15% decrease com-

Table 2. Treatment Progression Related to HbA1c in Patients With Type 2 Diabetes Mellitus#

Treatment	Baseline		Week-12			Week-26		
	n (%)	HbA1c	n (%)	HbA1c	HbA1c < 7%	n (%)	HbA1c	HbA1c < 7%
Metformin	80 (6.0)	8.8 ± 1.6	61 (4.6)	7.4 ± 1.0	17 (27.9)	49 (3.8)	6.9 ± 0.9	27 (55.1)
Sulfonylurea	94 (7.0)	9.1 ± 2.0	60 (4.6)	7.6 ± 1.3	19 (31.7)	54 (4.2)	6.9 ± 0.8	34 (63.0)
Metformin and sulfonylurea	710 (52.8)	9.4 ± 1.6	528 (40.1)	8.1 ± 1.4	76 (14.4)	443 (34.3)	7.2 ± 0.8	170 (38.4)
Insulin*	460 (34.2)	10.3 ± 1.9	667 (50.7)	8.8 ± 1.5	30 (4.5)	746 (57.7)	7.7 ± 1.3	188 (25.2)
Total	1,344 (100)	9.7 ± 1.8	1,316 (100)	8.4 ± 1.5	142 (10.8)	1,292 (100)	7.5 ± 1.2†	419 (32.4)‡

HbA1c is expressed as the mean (± SD) while HbA1c < 7% is expressed as n (%). #Data are presented for 1,344 patients with HbA1c values available at baseline (33 patients had no baseline HbA1c value). *With or without metformin and sulfonylurea. †P < 0.001 from paired samples in *t*-test compared between final visit and baseline. ‡P < 0.001 from Chi-square test.

pared to baseline) and a precision of 2% (using $n = px(1 - p) \times (1.96/e)^2$), the minimum sample size was 1,224 patients (confidence interval (CI) of 95%). Thus, each participating center was expected to enroll 10 consecutive patients.

Measurements and data collection

Demographic and clinical data were collected from the patients' medical records. The following data were recorded at the inclusion visit: age, sex, weight, height, waist circumference, blood pressure, duration of T2DM, previous treatment(s) for diabetes, treatment duration, treatment doses, fasting blood glucose (FBG) and HbA1c. HbA1c, FBG, body mass index (BMI), waist circumference and changes in treatment doses were recorded at the two follow-up visits.

Statistical analysis

Continuous variables are summarized as means ± SD and categorical variables are presented as percentages. When comparing groups, the *t*-test was used to assess the statistical significance of differences between means and the Chi-square test was used to assess the statistical differences between percentages. A P value of ≤ 0.05 was considered statistically significant. SPSS version 17.0 was used for all statistical analyses.

Results

Study population

A total of 139 centers agreed to participate in the study and 1,377 patients were enrolled. Table 1 summarizes the sociodemographic and clinical characteristics of the patients by diabetes treatment at baseline (inclusion). Mean age of the patients was 56.6 ± 10.1 years (range: 19 - 98), mean duration of T2DM was 8.0 ± 5.6 years (range: 0 - 46), mean weight was 77.4 ± 12.2 kg (range: 45 - 145) and mean BMI was 28.3 ± 4.7 (kg/m^2) (range: 18 - 38).

Patients already receiving treatment with insulin at baseline in addition to metformin and/or sulfonylurea had a significantly longer duration of diabetes than those treated with metformin and/or sulfonylurea only (10.2 ± 5.6 vs. 6.8 ± 5.3 years, respectively, P < 0.001), significantly higher blood pressure, a greater incidence of cardiovascular and microvascular complications, and significantly higher HbA1c and FBG (Table 1). These observations are consistent with their longer duration of diabetes.

Diabetes treatment and glycemic control at inclusion

At inclusion, two-thirds of patients (66.1%) were using metformin and sulfonylurea separately or in combination to treat their diabetes and 33.9% were using metformin and/or sulfonylurea combined with insulin (Table 1). Metformin and sulfonylurea were most often used in combination rather than either of these two therapies alone.

Mean baseline HbA1c was 9.7±1.8% (range: 4.1 - 17.5). The main reason for not achieving glycemic control at the inclusion visit was non-observance of lifestyle recommendations (66.3% of patients), followed by a lack of efficacy of treatment (63.2%), a lack of diabetes education (59.3%) and poor treatment compliance (37.1%).

Diabetes treatment and glycemic control during follow-up

Insulin treatment was prescribed to 467 patients (33.9%) at the inclusion visit, mainly as a basal regimen. One of these patients was lost to follow-up at 26 weeks. Insulin treatment was initiated in 37.8% of patients at visit 2 and in 31.6% at visit 3. Starting insulin was associated with a higher HbA1c at inclusion. For the 910 patients on OADs without insulin at baseline, 330 (36.3%) progressed to insulin use within 26 weeks and 578 (63.5%) remained on metformin and/or sulfonylurea without insulin. Two patients were lost to follow-up at 26 weeks. No serious adverse events were reported for any patient.

Mean HbA1c decreased significantly (P < 0.001) from 9.7±1.8% at inclusion (n = 1,344) to 8.4±1.5% at 12 weeks (n = 1,316) and 7.5±1.2% at the 6-month follow-up (n = 1,292) (Table 2). The proportion of patients with controlled glycemia increased significantly from 10.8% at 12 weeks to 32.4% at 26 weeks (P < 0.001).

The mean doses of the three anti-hypoglycemic drugs at inclusion and at 26 weeks are shown in Table 3. It can be seen that the mean dose of metformin increased significantly in all three groups between baseline and week 26 and the mean insulin dose also increased significantly in those patients receiving insulin at baseline.

Patients treated with metformin and sulfonylurea without insulin during follow-up had a mean decrease in HbA1c of -1.8% (P < 0.001) at 26 weeks (Table 3). In contrast, mean HbA1c decreased from 10.3% at inclusion to 7.6% at 26 weeks in those receiving insulin therapy at baseline (mean difference, -2.7%, P < 0.001). For those who were started on insulin therapy during follow-up, mean HbA1c decreased from 9.9% to 7.8% at 26 weeks (mean difference, -2.1%, P < 0.001). This improvement in HbA1c was accompanied by a significant increase in mean dose of metformin and insulin over the 26 weeks (Table 3). Mean FBG, weight, waist circumference and blood pressure decreased significantly over the study period in all three groups except for waist measurement in the group that was receiving insulin therapy at baseline. Mean weight of patients already receiving insulin at baseline was 77.5 kg. This decreased to 76.5 kg (mean decrease of -1.0 kg) at 26 weeks (Table 3) (P = 0.003). Mean weight also decreased significantly from 78.1 to 75.6 kg over the 26-week period in the group treated with metformin and/or sulfonylurea without insulin (mean difference, -2.5%, P < 0.001) and from 77.6 to 75.6 kg (mean difference, -2.0 kg, P < 0.001) in the group where insulin was added during the 6-month observation period.

Reasons for a lack of glycemic control during follow-up (at end of study) were assessed during the last visit. The main reasons were non-observance with lifestyle recommendations (22.0%), no efficacy of treatment (14.8%), lack of compliance

Table 3. Treatment Progression in the Three Groups of T2DM Patients

Characteristics	Metformin and/or sulfonylurea at baseline				Insulin* at baseline (n = 466)	
	Maintained on Met and/or Sulf (n = 576)		Progressed to insulin* (n = 330)			
	Baseline	Week 26	Baseline	Week 26	Baseline	Week 26
HbA1c (%)	8.9 (1.5)	7.1 (0.8)†	9.9 (1.7)	7.8 (1.2)†	10.3 (1.9)	7.6 (1.2)†
FBG (mg/dL)	222.6 (66.5)	133.0 (32.1)†	252.1 (70.8)	159.7 (48.3)†	268.4 (79.2)	144.5 (44.3)†
Dose of metformin (mg)	1,367 ± 728	1,552 ± 765†	1,645 ± 735	1,774 ± 706†	1,669 ± 706	1,708 ± 710‡
Dose of sulfonylurea (mg)	10 ± 23	11 ± 24	14 ± 27	15 ± 29	14 ± 28	13 ± 26
Dose of insulin glargine (IU)	-	-	-	15 ± 5	14 ± 6	19 ± 7†
Weight (kg)	78.1 (11.9)	75.6 (10.8)†	77.6 (12.6)	75.6 (11.3)†	77.5 (12.3)	76.5 (11.5)§
Waist circumference (cm)	98.6 (13.1)	95.7 (12.9)†	98.7 (14.6)	95.9 (16.0)†	96.2 (15.4)	95.6 (18.0)
Blood pressure (mm Hg)						
Systolic	140.0 (19.8)	132.3 (14.3)†	143.3 (21.7)	134.8 (14.1)†	147.6 (23.1)	134.1 (13.2)†
Diastolic	81.6 (12.1)	78.0 (9.2)†	82.5 (12.0)	79.0 (8.2)†	84.1 (11.7)	77.7 (8.4)†

Data are expressed as mean (± SD). FBG: fasting blood glucose. *With or without metformin and sulfonylurea. †P < 0.001, §P < 0.01 and ‡P = 0.01 from a paired-sample *t*-test.

with therapy (11.5%) and lack of diabetes education (9.1%). In univariate analysis, uncontrolled glycemia during the follow-up period was significantly associated with obesity, hypertension, dyslipidemia, use of one OAD treatment only and no insulin therapy (Table 4).

Discussion

This is the first non-interventional, observational study from Morocco to report on glycemic control in a large sample of patients with uncontrolled T2DM treated with metformin and/or sulfonylurea with or without insulin. After 26 weeks of treatment, the proportion of patients with optimal glycemic control was 32.4% according to the ADA definition (HbA1c < 7.0%). Baseline HbA1c overall was poor: 9.7±1.8%. At 26 weeks, improvement was -2.2% (±1.7%) in the entire cohort, -1.8% (±1.4%) in users of ODAs only and -2.7% (±1.9%) in users of ODAs + insulin. Despite the intensification of therapy with metformin, sulfonylurea and insulin, mean weight decreased over 26 weeks in insulin users and non-users.

Table 4. Association Between HbA1c Levels at 26 Weeks and Patient Characteristics

	HbA1c		P
	< 7%	≥ 7%	
Sex (F/M)	227/192	504/363	0.180
Obesity (yes/no)	117/297	292/557	0.029
Diabetes familial history (yes/no)	229/186	518/346	0.105
Hypertension (yes/no)	197/206	468/374	0.027
Dyslipidemia (yes/no)	167/213	430/349	0.000
Smoking (yes/no)	75/321	160/649	0.730
Self-monitoring glycemia (yes/no)	144/270	273/571	0.388
OAD (1 vs. 2)	112/294	175/652	0.012
Insulin therapy (yes/no)	116/269	289/493	0.021

Data are number.

Several recent observational studies have also demonstrated an improvement in glycemic control over 6 months to 5 years in patients with T2DM on OADs or insulin [10-15]. However, in these studies, there was a significant problem of weight gain and hypoglycemia. Therefore, insulin and OADs that achieve glycemic control without weight gain or hypoglycemia represent optimal therapy for T2DM [16]. Clinical trials show that insulin analog regimens enable glycemic targets to be achieved with potentially less risk of hypoglycemia and more convenient dosing [17]. Furthermore, patients with T2DM are less susceptible to hypoglycemia than those with type 1 diabetes [18]. Treatment intensification was shown to be effective since the addition of insulin to metformin and/or sulfonylurea or a combination of metformin and sulfonylurea led to a reduction in HbA1c levels in patients with uncontrolled T2DM [10, 12, 19, 20]. Conthe et al reported that after 1 year of treatment intensification (44.1% of combinations were metformin + sulfonylurea), mean HbA1c decreased significantly from 8.1% to 7.0% and the percentage of patients with glycemic control (HbA1c < 7%) increased from 12.2% to 51.6% [12].

Optimal glycemic control was recorded in 32.4% of our patients at their final visit (26 weeks). Such a level of control is consistent with the results of many studies. Reports from Saudi Arabia [21], United Arab Emirates [22, 23], Spain [24] and Jordan [25] show that, respectively, 24-27%, 32-34%, 34.6% and 34.9% of people with diabetes were achieving control targets. In Kuwait, only 16-18% of patients achieved the goal of HbA1c < 7% [26, 27]. These authors explained this by poor eating habits, poor compliance with medication and the use of inappropriate herbal medicines. In another study from Jor-

dan [28], the percentage of patients with optimal control only increased slightly from 25.4% at the first visit to 27.5% at 12 months follow-up. These authors explained this by a lack of resources and educational efforts regarding diet and weight. In the CHOICE study carried out over 12 months in six European countries and looking at changes to treatment and outcomes, the percentage of patients in the insulin cohort with HbA1c < 7% increased from 5.1% at baseline to 32.2% [29]. In a meta-analysis, evaluating the benefits of initiating insulin glargine following the failure of metformin/sulfonylurea mono- or combined therapy, 68.1%, 50.4% and 56.4% achieved HbA1c ≤ 7.0%, respectively [30]. This study was a pooled analysis of 11 prospective, randomized clinical trials, including 2,171 adults with uncontrolled T2DM starting insulin glargine following a specific titration algorithm. In our insulin cohort, the percentage of patients with optimal glycemic control at 26 weeks was moderate (25.2%), perhaps because no specific titration algorithm was followed. Using of a specific titration algorithm could have been a method to improve glycemic control in our study.

Our findings are consistent with those of the A1chieve study, which was a follow-up study involving a cohort of 66,726 patients with T2DM, which included insulin and both insulin users and non-users [11]. In the A1chieve study, the percentage of participants achieving an HbA1c < 7.0% increased from 3.9% at baseline to 31.8% at week 24. In our study cohort, mean HbA1c at baseline was poor: 9.7 ± 1.8%. At 26 weeks, improvement was -2.2% (±1.7) in the entire cohort, and -2.1% (±1.7) and -1.8% (±1.7) for previous insulin-naive and insulin users, respectively. In North Africa, mean HbA1c decreased significantly from 9.5±1.8% to 7.9±1.4%. In a recent real-world study from the USA, an electronic medical record database for adult patients with T2DM showed that during follow-up (> 1 year), patients initiating insulin glargine had a greater change in HbA1c (-1.1%) [31]. In the CHOICE study, glycemic control was improved in patients starting insulin by a mean absolute reduction in HbA1c of -1.8% (±1.8) [29]. The decrease in HbA1c levels in our study during follow-up suggests that many of our patients may have received diabetic education and optimum management. On the other hand, it is known that achieving and maintaining HbA1c levels < 7% is difficult in patients with a longer duration of diabetes mellitus and the moderate diabetes duration in our study (8.0 ± 5.6 years) may be an alternative explanation.

Metformin is the first-line treatment for patients with diabetes because it is associated with reduced mortality rates and BMI and results in effective glucose control, lowering HbA1c by approximately 1% [7]. On the other hand, sulfonylurea causes hypoglycemia and modest weight gain [32]. The addition of sulfonylurea to metformin is unlikely to bring about a greater reduction in HbA1c levels than 1%. Even after titration to maximum tolerated doses [33], symptomatic hypoglycemia and weight gain may be experienced. In a meta-analysis, comparing the efficacy of add-on anti-hyperglycemic drugs in patients with T2DM that were not controlled with metformin and sulfonylurea, a weight increase was seen with insulin (2.8 kg) [34]. Commonly, the achievement and maintenance of glycemic control over time is associated with weight gain [35-37]. However, in our study mean weight decreased significantly, even in the insulin cohort. Nevertheless, the waist circumference of our patients on insulin did not change significantly. In our study, no specific education was recommended in the protocol. However, this result may be explained by educational efforts regarding diet during follow-up, which, together with a lack in weight gain, also resulted in a reduction in blood pressure and FBG.

The present study has several limitations. Detailed data about some aspects of patient management such as physical activity levels, concomitants medication, incidence of hypoglycemia and dietary intake were not available. All of these are likely to influence glycemic control. In particular, hypoglycemia, which frequently occurred in patients treated with sulfonylurea and insulin, and lipid profile were not controlled. Furthermore, this study addressed the outcome after 26 weeks of treatment. The impact on longer-term outcomes such as clinical complications or death was not assessed. A prospective, longer follow-up study than the current 26 weeks and more comprehensive information on all relevant variables is needed to clarify these limitations.

In summary, a significant number of patients with T2DM receive OAD treatment for many years despite a lack of glycemic control. The most frequent reasons for not achieving glycemic control are non-observance of lifestyle recommendations, lack of treatment efficacy, poor treatment compliance and a lack of diabetes education. Our study shows that initiating a basal insulin regimen in patients with T2DM not controlled with one or two OADs is effective at improving glycemic control. There is therefore a need to support patient education and to actively promote treatment for T2DM with metformin, sulfonylurea and insulin in routine clinical practice.

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Conflicts of Interest

N.E. and G.E. received grant support and/or served as a consultant for Sanofi, Eli Lilly, Novo Nordisk, MSD and AstraZeneca. A.C. and S.E. received grant support and/or served as a consultant for Sanofi, Eli Lilly, Novo Nordisk, Servier, MSD, Abbott, Novartis and AstraZeneca. Y.E. and C.N. declare no conflicts of interest. M.S. is employed at Sanofi Maroc.

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