

Original article

Glycemic Control Among Type 2 Diabetic Patients in Misurata, LibyaAbdallah Mahjoub^{*}, Khawla Hriba^{*}, Safaa Farhat^{*}

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Corresponding author: aamahjoub@gmail.com**Abstract**

Achieving an HbA1c level of less than 7% is the most important target in the management of diabetes mellitus. This study aimed to assess the glycemic control in ambulatory diabetic patients in Misurata, Libya, and the factors affecting the glycemic control in those patients. The study also aimed to describe the drugs used in the management of diabetic patients and the factors that influence the selection. A cross-sectional study was conducted on ambulatory diabetic patients in Misurata. Data were collected by reviewing the patients' medical records and conducting interviews with the patients themselves. Data were analyzed by IBM SPSS Statistical version 27. A p-value of less than 0.05 was considered statistically significant. During the study period, 193 patients, predominantly females (73.6%), were included. Metformin, insulin, sulfonylureas, and DPP4 inhibitors were the most prescribed drugs. Use of metformin and sulfonylureas was significantly higher among patients with a diabetic duration of less than 5 years, whereas the use of insulin was significantly higher among patients with a diabetic duration of more than 5 years. Creatinine clearance was significantly higher among patients who used metformin, sulfonylureas, or DPP4 inhibitors compared to those patients who didn't use these drugs. The median (IQR) of HbA1c in this study was 7.8 (2.05) %, and only 23.9 % of the patients achieved the target HbA1c level of < 7%. Poor glycemic control was significantly associated with diabetic duration of > 5 years and the use of insulin.

Keywords. Glycemic Control, Type 2 Diabetic Patients, Misurata, Libya.

Introduction

Diabetes mellitus is one of the most prevalent chronic illnesses worldwide. The world's estimates of type 2 diabetes in 2021 were 10.50% and expected to reach 12.20% by the year 2045 [1]. In Libya, in the year 2000, it was estimated that 14% of the people over 20 years had diabetes [2]. Diabetes mellitus is known for its long-term complications, which have been broadly classified as microvascular and macrovascular complications [3].

Microvascular complications include neuropathy, retinopathy, and nephropathy. Macrovascular complications include coronary heart disease, stroke, and peripheral vascular disease. Tight glycemic control plays an important role in preventing and slowing the progression of these complications. A Large number of well-controlled randomized clinical trials have addressed the effect of glycemic control in preventing the microvascular and macrovascular complications of diabetes mellitus. Many of these studies have proven the protective effect of tight glycemic control in preventing and retarding the progression of diabetic complications, especially the microvascular complications [4-13]. Based on this fact, tight glycemic control becomes the major target in the management of diabetic patients. Target glycemic control was defined by the American diabetic association (ADA) as glycosylated hemoglobin A1c (HbA1c) of less than 7%, pre-prandial plasma glucose level of 80–130 mg/dL, and peak postprandial plasma glucose level of <180 mg/dL [14]. Glycemic control is influenced by many factors, such as the diet and physical activity pattern of the patients, the prescribed drugs, and patients' adherence, as well as duration of the disease and other co-morbidities and concomitant drugs [15-17]. In this study, we aimed to evaluate the glycemic control among ambulatory type 2 diabetic patients in Misurata, Libya, and to assess the impact of different types of antidiabetic drugs on glycemic control.

Methods

This study was a prospective cross-sectional study conducted on ambulatory diabetic patients who seek medical follow-up at Misurata specialized center for diabetes and endocrine clinic and Zawiyat Al-Mahjoub Polyclinic in Misurata, Libya, during the period from 13th of March 2024 to 9th October 2024. Permission to conduct the study was obtained from the Faculty of Pharmacy, Misurata University, Libya. The ethical committee in the Misurata specialized center for diabetes and endocrine clinic, and Zawiyat Al-Mahjoub Polyclinic in Misurata have approved the study. The study and its purpose were explained to every eligible patient, and patients who agreed to participate signed an informed consent form. Data were collected by reviewing the patients' medical records and conducting interviews with the patients themselves. The recorded data include: demographic characteristics such as age, gender, body weight, antidiabetic drugs with their doses and frequency, glycemic control indicated by previous and current HbA1c, and FBG, other medical problems, and other concomitant drugs, and relevant laboratory investigations. Data were analyzed by IBM SPSS Statistical version 27. A p-value of less than 0.05 was considered statistically significant. Qualitative data were expressed as mean \pm SD or median with interquartile range (IQR), depending on the normality of their distribution. Normality of the data distribution was assessed by the Shapiro-Wilk test, as

it is the most reliable test of normality [18]. Categorical variables were presented as frequencies and percentages (%). The association between 2 categorical variables was assessed by cross-tabulation with chi-square or Fisher's exact test as appropriate. The association between 2 quantitative variables was assessed by the correlation coefficient with either Pearson correlation or non-parametric correlation with Spearman's correlation. The difference in one quantitative variable between 2 or more groups was assessed by parametric tests with the t-test or ANOVA, or non-parametric tests with the Mann-Whitney U test or Kruskal-Wallis test as appropriate.

Results

Patients' characters

The study included 193 participants with type 2 diabetes, of whom 51 (26.40%) were males and 142 (73.60%) were females. The patients' ages ranged from 28 to 90 years, with a mean \pm SD of 61.9 ± 11.2 years. Demographic characteristics of patients are shown in Table 1. The median duration of diabetes in the participants was 13 years. Among the study population, 134 patients (70.90%) have at least one comorbidity. Specifically, 96 patients (50.70%) have hypertension, 69 patients (36.60%) have dyslipidemia, 19 patients (10%) have CHD, and 4 patients (2.10%) have gout. These comorbidities occurred either individually or in combination with other conditions in the same patient. Only 55 participants (29.10%) had no comorbidities. Unfortunately, many of the essential laboratory investigations were not available. However, Total cholesterol, triglycerides, urea, and creatinine blood levels were available for most of the patients. These data are presented in Table 2.

Table 1. Patients' characteristics.

Patients' Characteristics		Value
Age, years, Mean \pm (SD)		61.9 \pm 11.2 years
Weight, Kg Median (IQR)		80 (20.5)
Duration of diabetes, years, median (IQR)		13 (10)
Gender	Male n (%)	51 (26.40%)
	Female n (%)	142 (73.60%)
Comorbidity	No other co-morbidity, n (%)	55 (29.10%)
	Hypertension, n (%)	96 (50.70%)
	Dyslipidemia, n (%)	69 (36.60%)
	Chronic heart diseases, n (%)	19 (10%)
	Gout, n (%)	4 (2.10%)
	Others, n (%)	34 (18%)

Table 2. Laboratory investigation of lipid profile and renal function test

Lab test	Number of patients	Distribution	Mean \pm SD	Median (IQR)
Total cholesterol	157	Normal	168.82 \pm 43.67	
Triglycerides	164	Not normal		137 (97.75)
Urea	168	Not normal		33.13 (16.4)
Creatinine	166	Not normal		0.695 (0.37)
Creatinine clearance	166	Not normal		100.8 (97.17)

Use of antidiabetic drugs

All of the included patients were under pharmacological management of diabetes mellitus. However, different classes of drugs were used by the study's participants. The majority of the participants, 103 (53.40%) were treated by a combination of oral antidiabetic medication and subcutaneous insulin injection. Sixty-three (63; 32.60%) patients were using oral antidiabetic medication only, and the rest 27 (14%) patients were using subcutaneous insulin only. (Table 3) represents the use of different antidiabetic drugs and regimens in this study. Metformin was the most frequently prescribed drug, as it was used by 83.4% of the patients, followed by insulin (67.40%).

Table 3. Uses of different antidiabetic drugs by the study participants

Anti-diabetic drugs	Frequency (%) of users	Antidiabetic regimens	Frequency (%) of users
Metformin	160 (83.40%)	Insulin + Metformin	72 (37.30%)
Insulin	130 (67.40%)	Insulin only	28 (14.50%)
Sulfonylureas	39 (23.30%)	Sulfonylurea + Metformin	26 (13.50%)
Dipeptidyl peptidase 4 inhibitors (DPP4Is)	35 (18.10%)	Metformin only	19 (9.80%)
Sodium-Glucose Transport 2 (SGLT2) Inhibitors	11 (5.70%)	Insulin + Metformin + DPP4i	15 (7.80%)
		Sulfonylurea + Metformin + DPP4Is	12 (6.20%)
		Others	21 (10.90%)

The total daily dose of insulin ranges from 10 IU to 120 IU, with a mean \pm SD of 50.75 \pm 20.66 IU. The total daily insulin as IU/kg was in the range of 0.11 to 1.25 IU/Kg, with a mean of 0.6 \pm 0.23 IU/Kg. Metformin doses range from 500 mg/day to 2550 mg/day.

Factors influencing the use of antidiabetic drugs

Use of some antidiabetic drugs was significantly associated with the duration of diabetes. Use of metformin and sulfonylureas was significantly higher among patients who had diabetes for less than 5 years. On the other hand, the use of insulin was significantly higher among patients who had diabetes for more than 5 years. (Table 4) summarizes the relation between the duration of diabetes mellitus and the use of some antidiabetic drugs.

Creatinine clearance was significantly higher among patients who used metformin, sulfonylureas, or DPP4Is compared to patients who did not use these medications. Furthermore, the use of metformin was significantly higher among patients with CrCL > 30ml/min compared with patients with CrCL \leq 30 ml/min (87.3% vs 68.8%, $P = 0.011$). On the other hand, creatinine clearance was lower among patients who use insulin therapy; however, this difference was statistically insignificant (Table 5).

Other patients' factors such as gender, age, and weight did not show a significant effect on the use of the antidiabetic regimen. Although not statistically significant, sulfonylureas were prescribed more commonly to non-elderly patients compared to elderly patients (27.8% vs 16.7%, $P = 0.071$). Similarly, the presence of common co-morbidities such as hypertension, hyperlipidemia, and CHD didn't show a significant influence on the use of different antidiabetic drugs.

Table 4. The relation between antidiabetic regimens and the duration of diabetes mellitus

Antidiabetic drugs	Less than 5 years (24 Patients)	5 years or more (165 patients)	Person Chi-square (P value)
Metformin	24 (100%)	134 (81.20%)	$P = 0.020$
Insulin	5 (20.80%)	123 (74.50%)	$P = 0.000$
Sulfonylureas	12 (50%)	32 (19.40%)	$P = 0.001$
DDP4Is	7 (29.20%)	28 (17%)	$P = 0.151$
Gliflozins	0 (0.00%)	10 (6.10%)	$P = 0.215$

Table 5. creatinine clearance according to the use of antidiabetic drugs

Antidiabetic drugs		Number of patients	Creatinine clearance	Mann-Whitney Test (P value)
Metformin	Used	139	106.7(78.5)	$P = 0.046$
	Not used	27	67.26 (151.7)	
Insulin	Used	110	92.4 (108.8)	$P = 0.106$
	Not used	56	112.3 (64)	
Sulfonylureas	Used	44	117(66.6)	$P = 0.022$
	Not used	122	90.75(98.8)	
DDP4Is	Used	32	125 (83.4)	$P = 0.007$
	Not used	134	95.7(100.5)	

Glycemic control

The median (IQR) of HbA1c in the recent and previous evaluation was 7.8 (2.05) % and 8.14 (2.32) %, respectively. The median (IQR) of current and previous FBG were 158 (81.20) mg/dL and 166 (74.5) mg/dL, respectively.

Only 34 patients (23.90%) have achieved the target HbA1c of less than 7%, while 44 (31%) patients had HbA1c between 7 and 8%, and 64 (45.10%) patients had HbA1c more than 8%. Regarding the FBG, only 50 (26.70%) patients had their FBG at the target recommended range of 80 -130 mg/dL.

Effects of antidiabetic regimen on glycemic control

The HbA1c was significantly higher among the patients who used insulin compared to the patients who did not use insulin (Table 6). These differences were statistically significant by the Mann-Whitney U test. Similarly, the proportion of patients who had achieved the target HbA1c was smaller among the patients who used insulin (18.7 vs 33.30%). This difference was statistically significant by the Chi-square test ($\chi^2 = 3.853$, $df = 1$, $P = 0.05$). Furthermore, there was a significant positive correlation between the total daily insulin dose and the value of HbA1c ($r = 0.256$, $P = 0.015$). However, use of other antidiabetic drugs was not associated with a significant difference in the median HbA1c or the proportion of patients who achieved the target HbA1c (Table 6).

Effect of changing the antidiabetic regimen on the glycemic control

Among the 193 participants, 92 (47.70%) patients had their current antidiabetic regimen exactly as the previous regimen, whereas 47 (24.40%) had their current regimen intensified by increasing the doses of previous drugs, addition of other drugs, or both. On the other hand, 40 (20.70%) had their regimen lessened by removing or reducing the doses of some drugs. However, in 14 (7.30%) patients, the change in the regimen was difficult to categorize because it involved the addition of some drugs and reducing the dose of some other drugs or withdrawal of some drugs and increasing the dose of other drugs. The effect of changing the antidiabetic regimen on the changes of HbA1c is shown in (Table 7). As expected, intensifying the regimen leads to more reduction in the HbA1c; however, this difference was statistically insignificant ($P = 0.518$), and the magnitude of this improvement was very small.

Table 6. Effect of antidiabetic drugs on glycemic control

Antidiabetic drugs		Number of patients	HbA1c Media (IQR)	Mann-Whitney Test (P value)	% of patients who achieved the target HbA1c	Chi-Square test (P value)
Metformin	Used	117	7.97 (2.01) %	0.853	24.40 %	0.78
	Not used	21	7.77 (2.72) %		21.70%	
Insulin	Used	87	8.30 (2.70) %	0.001	18.70 %	0.05
	Not used	51	7.60 (1.40) %		33.30%	
Sulfonylureas	Used	36	7.72 (1.68) %	0.342	27.80 %	0.53
	Not used	102	7.79 (2.15) %		22.60%	
DDP4Is	Used	27	7.74 (1.53) %	0.93	22.20%	0.81
	Not used	111	7.89 (2.10) %		24.30%	

Table7. The effect of changing the antidiabetic regimen on the HbA1c levels.

Change in anti-diabetic regimen	Changing in HbA1c (Previous HbA1c – Current HbA1c) Mean \pm SD	Comment
Intensifying	0.44 \pm 1.4 %	Improvement
Same regimen	0.17 \pm 1.32 %	Improvement
Lessening	- 0.03 \pm 1.35%	Worsening
Statistical test	One-Way ANOVA (P 0.518)	

Factors affecting glycemic control

The median (IQR) of HbA1c for individuals with a diabetes duration of less than 5 years was 7.3 (1.39) %, which indicates relatively better glycemic control compared to the HbA1c for those with a duration of diabetes longer than 5 years (8.0 (2.15)) %. This difference was statistically significant by the Mann-Whitney test ($p = 0.016$). Furthermore, the % of patients who achieved the target HbA1c was slightly higher among the patients with a duration of diabetes less than 5 years compared with those of diabetes duration longer than 5 years (34.8% vs 21.7%). However, this difference was statistically insignificant by the Pearson Chi-Square test ($p = 0.181$). The analysis of HbA1c levels reveals a slight difference between males and females. The median (IQR) of HbA1c values was 7.65 (1.9) % in males and 8.00 (2.18) % in females. However, this difference was statistically insignificant by the Mann-Whitney U test ($p = 0.1$). Furthermore, the % of patients who achieved the target HbA1c level of less than 7% was slightly and insignificantly different between male

and female patients (29.2% vs 21.3%, $P = 0.297$). Similarly, the correlation coefficient (r) of -0.15 and the P value of 0.142 indicate a small statistically insignificant negative correlation between the age of the patients and the value of HbA1c. Furthermore, there was a slight and statistically insignificant difference between the median HbA1c in elderly and non-elderly patients [7.7 (1.86) % vs 7.9 (2.49) %, $P = 0.377$]. The relationship between HbA1c levels and weight was found to be very weak and statistically insignificant, as indicated by a correlation coefficient of (0.014) and a p -value of (0.876), which indicates that weight does not have a significant effect on HbA1c values.

Discussion

Type 2 DM is a chronic progressive disease, which depends on pharmacological and non-pharmacological therapy for its management. Non-pharmacological therapy, represented by diet control and physical exercise, is central to the management of this disease, especially in the initial period [19]. However, as the disease progresses, pharmacological treatment becomes crucial for glycemic control. In our study, metformin was the most prescribed drug, followed by insulin.

Metformin is a very important drug in the management of Type 2 diabetes mellitus. It is still considered the drug of choice in the treatment of T2 DM by many global clinical practice guidelines [20, 21]. Its role in the prevention of microvascular and macrovascular complications of diabetes was proven in a large, well-controlled clinical trial [22]. Furthermore, metformin has the advantage of being a weight-neutral, euglycemic agent, which favors its use in obese diabetic patients and in patients in whom hypoglycemia could be more serious, such as elderly patients [22 – 24]. Metformin is eliminated unchanged in the urine by filtration and active tubular secretion, and its elimination is highly correlated with creatinine clearance [25,26]. Clinical practice guidelines differ in their recommendation regarding the use of metformin in the setting of impaired renal function. For instance, Food and Drug Administration prescribing guidelines consider metformin as a contraindication in men and women with serum creatinine ≥ 1.5 mg/dL or 1.4 mg/dL, respectively [20].

The American Diabetes Association and European Association for the Study of Diabetes report that metformin seems safe unless eGFR falls to less than 30 mL/min per 1.73 m² [27]. Because it is difficult to estimate the GFR, we use creatinine clearance as an estimation of renal function. Although creatinine clearance can overestimate the GFR by about 10 - 20 %, it is considered a practical alternative for GFR [28]. In this study, we found a significant difference in the creatinine clearance between patients who used metformin and those who were not prescribed this drug. Also, the % of patients who use metformin was significantly higher among patients with creatinine clearance > 30 ml/min compared with patients with creatinine clearance ≤ 30 ml/min. Likewise, the creatinine clearance was significantly higher in patients who used sulfonylureas and DPP4Is compared with patients who did not use these medications. Sulfonylureas were associated with increased risk of hypoglycemia in patients with renal impairment and were recommended not to be used in patients with creatinine clearance ≤ 30 ml/min [29 - 31]. DPP4Is such as sitagliptin and vildagliptin have an important role in the management of T2DM and were not associated with increased body weight and hypoglycemia [30]. They are also effective in patients with renal impairment, but dose adjustment is required based on the degree of renal impairment [31,32]. In this study, only 35 (18.1%) patients used DPP4Is. only 1 patient among the 31 patients with creatinine clearance < 30 ml/min was prescribed one of these medications. While most available clinical data suggest a dose reduction of DPP4Is in renal impairment, abandonment of these agents just because of declined renal function is not recommended [31,32].

Insulin was the second most prescribed drug in this study. Although patients with T2DM can be managed effectively with oral antidiabetic agents, insulin is usually required for better glycemic control, especially in patients with poor adherence to lifestyle recommendations and in patients with long-standing T2DM [20, 21, 33, 34]. In our study, unlike oral antidiabetic agents, the use of insulin was significantly higher among patients with a diabetic duration longer than 5 years, which could be due to the deterioration in glycemic control by the progression of disease and aggressive decline in beta cell function over time, which necessitates the use of exogenous insulin [31]. Use of insulin was not significantly affected by the renal function status of the patients because insulin is considered the safest choice for patients with declining renal function, although the risk of hypoglycemia is higher in those patients [31, 35]. Although metformin and insulin were the most prescribed drugs in our study, which is according to the recommendation of global clinical practice guidelines [20, 21]. The pharmacological therapy should be aimed at reducing the cardiovascular risk in patients with established CHD or at high risk for CHD, such as patients with hypertension and high levels of LDL. Therefore, ADA recommended sodium-glucose transporter 2 inhibitors for the management of such patients [20]. However, in our study, we didn't find in significant effects of these co-morbidities on the selection of anti-diabetic agents.

Glycemic control is very important in the management of diabetes mellitus in order to slow the progression of the disease and its complications. Therefore, the global clinical practice guideline for the management of diabetes mellitus has set a measurable target that should be achieved to ensure the appropriate management of T2DM. One of the most important targets set by ADA and other practical guidelines is the

achievement of an HbA1c level of less than 7% [20, 21]. According to this context, the findings from our study reveal important insights into the management of diabetes in Misurata city. To our knowledge, this is the first study assessing the glycemic control in Misurata, Libya. The median HbA1c level of 7.8% in our cohort, with only 23.9% of patients reaching the target HbA1c of less than 7%, indicates a significant challenge in achieving optimal glycemic control. However, our finding regarding glycemic control is slightly better than what was found in previous Libyan studies. For instance, a study conducted in Tripoli, Libya, found that the mean HbA1c was 8.9%, with only 21.8% of patients achieving the target HbA1c below 7% [36]. Another study conducted in Benghazi reported a mean HbA1c of 9.4% and only about 14% of participants achieved good glycemic control [37]. Poor glycemic control was encountered in many studies conducted in various countries. For instance, a study conducted in Oman reported that 54% of patients met the target HbA1c [38]. In Lebanon, 31.8% of the patients had achieved the target HbA1c [38]. In Nigeria, 38% of the patients achieved the target HbA1c [40].

Many factors could influence the glycemic control in diabetic patients. One of the most important of these factors is adopting a healthy lifestyle with control of diet and regular exercise [41]. Unfortunately, in our study, we did not assess the dietary and physical activity of the participants, which could strongly influence the glycemic control. However, we did not find any significant effects of the age or gender of the patients, or the presence of any co-morbidity, on the level of HbA1c. However, our study reveals that glycemic control was significantly better among patients who had had diabetes for less than 5 years compared with patients with a diabetic duration longer than 5 years. This difference is expected because of the progressive nature of the disease and the corresponding decline in beta-cell function over time. Our results indicate that the use of insulin injection was associated with poor glycemic control. This unexpected result is difficult to explain; it is unlikely that the addition of insulin therapy will lead to deterioration in glycemic control. However, because insulin therapy was used more frequently in patients with a diabetic duration of more than 5 years, and on the other hand, the duration of diabetes itself is associated with poor glycemic control. It could be that the effect of insulin therapy on glycemic control is influenced by the duration of diabetes. Furthermore, the use of insulin in those patients could be a result (not the cause) of their poor glycemic control.

The role of insulin is well established in the management of both type 1 and type 2 DM [14, 15, 20, 34]. It is also important to mention that some studies have found that tight glycemic control is not recommended in patients with long-standing diabetes mellitus. For instance, Ghouse et al. found that the risk of death was increased with poorer glycemic control in patients with diabetes duration of <5 years, whereas the risk of death among the patients with diabetes duration of > 5 years was significantly lower among patients with HbA1c between 6.5 – 7.9 % compared with mean HbA1c < 6.5%. [42]. However, achieving good glycemic control requires good control of diet, weight management, physical activity, and adherence to the prescribed medication, and because all these factors were not assessed in our study, our results regarding the association between glycemic control and use of insulin should be interpreted with caution.

Conclusion

Our study revealed that the HbA1c in most of the ambulatory diabetic patients in Misurata is above the target level, especially among patients with longstanding diabetes, and in patients who are using insulin therapy either alone or in combination with various oral antidiabetic drugs. Our study also shows that metformin and insulin are still the most frequently used drugs for the management of T2DM, whereas the use of relatively new drugs such as DPP4Is or SGLT2 inhibitors is still very low. Our study also shows a significant relationship between the use of antidiabetic medication and the renal function of the patients

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Conflicts of interest

The authors declare no conflicts of interest

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