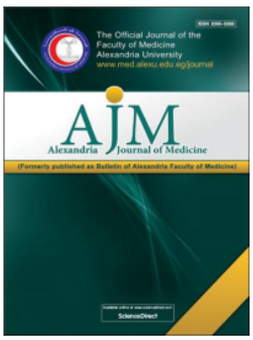

Alexandria Journal of Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/tajm20

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To cite this article: Jihad A. Haddad, Muwafaq A. Al Hyari, Monther S. Al Momani, Ahmad A. Al Omari, Fawaz L. Ammari & Firas O. Annabi (2020) Baseline characteristics and treatment pattern of type 2 diabetes patients in Jordan: analysis from the DISCOVER patient population, Alexandria Journal of Medicine, 56:1, 51-55, DOI: 10.1080/20905068.2020.1747733

To link to this article: https://doi.org/10.1080/20905068.2020.1747733

Published online: 26 May 2020.

ALEXANDRIA JOURNAL OF MEDICINE
2020, VOL. 56, NO. 1, 51–55
https://doi.org/10.1080/20905068.2020.1747733

Baseline characteristics and treatment pattern of type 2 diabetes patients in Jordan: analysis from the DISCOVER patient population

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ABSTRACT

Introduction: Jordan has limited published data on T2DM and its treatment patterns. This analysis of the DISCOVER study, focusing on Jordan, is aimed at describing the characteristics of patients and treatment patterns according to the real-world setting in T2DM patients initiating a second-line antidiabetic treatment

Methods: The DISCOVER study is an ongoing, multi-country, multicenter, observational, prospective, and longitudinal cohort study. The baseline data of patients' characteristics, clinical and laboratory variables, micro- and macro-complications, and treatment choices were captured on a standardized case report form.

Results: Two hundred and seventy-one patients were enrolled from 13 different clinical sites in Jordan. Sixty percent of the patients were male. The participants overall mean age was 53.8 ± 11.3 years with a mean BMI 30.8 ± 5.0 kg/m 2. The mean duration of T2DM was almost 6 years and the mean documented HbA1c and fasting plasma glucose were e 8.4% ± 1.6 and 180.9 ± 63.7 mg/dL, respectively, at the initiation of second-line antidiabetic treatment. Almost 25% of the participants were reported to be either current smokers or ex-smokers. More than 40% of patients had comorbidities such as hypertension or dyslipidemia. Diabetes related microvascular and macrovascular complications were documented in 10.3% and 12.5% of patients, respectively. Metformin (MET) alone was used as a first-line therapy in almost one-half of the patients and in combination with sulfonylurea (SU) in approximately one-third of the patients. The most commonly used second-line therapy was the combination of MET and dipeptidyl peptidase-4 inhibitors (DPP-4i) with 29.9% followed by the triple therapy of MET, SU, and DPP-4i with 28%.

Conclusion: A substantial number of patients were young with uncontrolled diabetes and at high risk for micro- and macrovascular complications. Therefore, a comprehensive management with early treatment intensification and risk factors modifications are required to achieve target goals.

ARTICLE HISTORY
Received 8 September 2019
Accepted 3 February 2020

KEYWORDS
DISCOVER study; type 2 diabetes mellitus; treatment; antidiabetic agents; oral glucose-lowering agents; second-line treatment; Jordan

1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) was estimated to be 425 million in 2017 and this number is projected to increase by almost 50% by 2045 [1]. Hyperglycemia is an important risk factor for the development of microvascular disease in patients with T2DM. T2DM is also considered to be a significant risk factor for cardiovascular disease – the most common cause of death in this patient population [2,3]. The global economic burden of diabetes is approximately 727 USD billion annually, which represents 12% of the global health expenditure [1].

In the Middle East region, the prevalence of T2DM is estimated to be 9.2%, which is considered the second highest region in the world [4]. There are almost 40 million people with T2DM in this region and it is predicted that this number will increase by more than two folds by 2045 [4]. In Jordan, there is limited published data on the incidence and the prevalence of T2DM. In 2008, Ajlouni et al showed that Jordan had a high prevalence of diabetes and impaired fasting glucose (IFG), reaching 24.9% [5]. However, the IDF shows that Jordan has a diabetes and IFG prevalence of 11.8% and 7.6, respectively [4]. Data on diabetes treatments and control is scarce, especially in the Middle East area. The available data sources do not have enough information to capture the entire patient journey.

The primary objective of the DISCOVERing Treatment Reality of Type 2 Diabetes in Real World Settings (DISCOVER) is to describe the disease management patterns and clinical evolution of T2DM patients initiating a second-line antidiabetic treatment, (add-on or switch) over the course of 3 years. The aim of this report is to describe the baseline data of T2D patients from Jordan cohort of the DISCOVER study.

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In this report, we describe the overall patient characteristics, treatment patterns for first- and second-line treatment, clinical parameters, prevalence of microvascular and macrovascular complications, and the risk factors associated with these complications.

2. Methods

The rationale and methods of the DISCOVER study were published elsewhere in details [6]. In brief, the DISCOVER study is a multi-country, multicenter, observational, prospective, longitudinal cohort study over 3-year period (ClinicalTrials.gov Identifier: NCT02322762). As part of the protocol, additional patients were allowed to be enrolled retrospectively, depending on approval timelines of certain countries. Patients with T2DM who were initiating a second line anti-diabetic therapy (add-on or switching) after a first-line oral treatment with a monotherapy, dual or triple therapy were eligible to participate in the study. The study was approved by the Institutional Review Board of each participating institution. After meeting the inclusion/exclusion criteria and signing an informed consent form, patients were included in the study. Electronic case report forms were utilized for data collection by the investigators in all participating countries, including Jordan. At the initial routine clinical visit, the baseline data included socioeconomic and demographic information, anthropometric measurements, laboratory values, previous medical history, including diabetes history and complications, comorbidities, first-line antidiabetic drug therapy and reason for change, second-line treatment choice and the reason for choosing such treatment, as well as patient-related outcomes, which we will not be discussed in this report. Data also will be captured at future routine clinical visits at 6, 12, 24, and 36 months, which is the end of the study.

Descriptive statistics were used for the demographic variables, patient characteristics, treatment patterns, HbA1C level, blood glucose level, lipid profile, body weight, body mass index (BMI), and blood pressure. The mean and the standard deviation were utilized for continuous data and categorical data were expressed as percentages.

3. Results

Two hundred and seventy-one patients were enrolled from Jordan in the DISCOVER study program. All patients were recruited from 8 private clinics and 5 government and university-based clinics in Jordan. The clinical sites were a mix of internal medicine (46.2%) and endocrinologists (53.8%) practices. The baseline social and demographic characteristics of the cohort are summarized in Table 1. Sixty and one-half percent of the patients were male. The participants overall mean age was 53.8 ± 11.3 years and 34.3% of them were reported to be unemployed. The vast majority of the patients were covered by either private or governmental insurance. More than one-half of study population had completed either a primary or secondary level of education and almost 43% of the participants completed university level of education.

The baseline characteristics of medical history, comorbidities, and diabetes related complications are presented in Table 2. The mean duration of diabetes was 5.98 ± 5.8 years and the mean HbA1c and the mean fasting plasma glucose (FPG) were documented

Table 1. Baseline social and demographic characteristics.

Parameter	N = 271
Sex, male- n (%)	164 (60.5%)
Age, years, mean±SD	53.8 ± 11.3
Main working status	
Employed	100 (36.9%)
Self-Employed	39 (14.4%)
Not working	93 (34.3%)
Retired	28 (10.3%)
Missing data	11 (4.0%)
Health insurance coverage	
Private	110 (40.6%)
Public/governmental	110 (40.6%)
Mixed	2 (0.74%)
No Insurance	36 (13.3%)
Missing data	13 (4.8%)
Education level	
No formal education	1 (0.4%)
Primary (1–6 years of education)	49 (18.1%)
Secondary (7–13 years of education)	96 (35.42%)
University/Higher Education (13+ yrs)	107 (39.5%)
Missing data	18 (6.6%)

Table 2. Baseline medical history, comorbidities, and complications characteristics.

Parameter	N = 271
HbA1c, % ± SD	8.4 ± 1.6
Fasting Glucose(mg/dL), mean ± SD	180.9 ± 63.9
Duration of diabetes (years), mean ± SD	5.98 ± 5.8
BMI, Kg/m^2	30.8 ± 5.1
Tobacco Smoking	
Nonsmoker	193 (71.2%)
Ex-smoker	17 (6.3%)
Current smoker	52 (19.2%)
Missing data	9 (3.3%)
Blood Pressure, mm Hg	
Systolic, mean ±SD	132.6 ± 16.5
Diastolic, mean ±SD	80.0 ± 10.0
Lipid Profile	
Total Cholesterol(mg/dL), mean ±SD	188.7 ± 48.6
LDL(mg/dL), mean ±SD	117.9 ± 46.3
HDL(mg/dL), mean ±SD	41.0 ± 10.6
Triglycerides(mg/dL), mean±SD	213.1 ± 176.3
Hypertension	111 (41.0%)
Hyperlipidemia	114 (42.1%)
Microvascular complications	28 (10.3%)
Chronic Kidney Disease	6 (2.2%)
Albuminuria	7 (2.6%)
Retinopathy	6 (2.2%)
Peripheral Neuropathy	9 (3.3%)
Autonomic Neuropathy	2 (0.7%)
Erectile Dysfunction	8 (3.0%)
Any Macrovascular Disease	34 (12.5%)
Heart Failure	3 (1.1%)
Coronary Artery Disease	26 (9.6%)
Myocardial Infarction	7 (2.6%)
Percutaneous Coronary Intervention	12 (4.4%)
Ischemic Stroke	5 (1.8%)

to be 8.4% ± 1.6 and 180.9 ± 63.9 mg/dL, respectively. Approximately 25% of the participants were reported to be either current smokers or ex-smokers and 75% of the patients had reported to be nonsmokers. More than 40% of patients had comorbidities such as hypertension or dyslipidemia. The mean systolic blood pressure was 132.6 ± 16.5 mm Hg and the mean LDL-C was 117.9 ± 46.3 mg/dL. Diabetes related microvascular and macrovascular complications were documented in 10.3% and 12.5% of the patients, respectively. The most commonly reported microvascular complication was peripheral neuropathy and the most commonly reported macrovascular complication was coronary artery disease.

More than half of the patients were initiated on monotherapy. Metformin alone or in combination with other oral antidiabetic agents were the most commonly prescribed therapies as a first-line treatment. Metformin alone was used as a first-line therapy in almost 50% of the patients and in combination with sulfonylurea in approximately one-third of the patients. The most commonly used second-line therapy was the combination of metformin and dipeptidyl peptidase-4 inhibitors (DPP-4i) with 29.9% followed by the triple therapy of metformin, sulfonylureas, and DPP-4i with 28% (Table 3). The most common reasons for changing first-line therapy were the lack of efficacy, weight gain, and physician preference. Efficacy, tolerability, weight, and hypoglycemia were the primary reasons reported for choosing the second-line therapy (Table 4).

Concomitant medications such as Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs) were the most frequent concomitant antihypertensive agents used in 34.3% of the cohort. Statins were the most frequently prescribed lipid lowering agents in 45.4% of the patients. Antiplatelet therapy, mainly aspirin, was used in almost one-quarter of the patients (Table 5).

Table 3. First- and second-line treatment characteristics.

First-line therapy	N = 271
Met (Mono)	127 (46.9%)
SU (Mono)	13 (4.8%)
DPP-4i (Mono)	1 (0.4%)
Other (Mono)	2 (0.7%)
Met+SU (Dual)	94 (34.7%)
Met+DPP-4i (Dual)	16 (5.9%)
Met+other (Dual)	6 (2.2%)
Other Dual therapy	5 (1.8%)
Met+SU+DPP-4i (Triple)	6 (2.2%)
Met+SU+TZD (Triple)	1 (0.4%)
Second-line therapy	
Met monotherapy	2 (0.7%)
DPP-4i (Mono)	16 (5.9%)
Met+SU (Dual)	22 (8.1%)
Met+DPP-4i (Dual)	81 (29.9%)
Met+other (Dual)	7 (2.6%)
SU+TZD (Dual)	7 (2.6%)
Other Dual therapy	3 (1.1%)
Met+SU+DPP-4i (Triple)	76 (28.0%)
Met+SU+TZD (Triple)	7 (2.6%)
Other Triple Therapy	6 (2.2%)
4 or 4+ Therapy	7 (2.6%)
Insulin (May also receive oral therapy)	37 (13.7%)

DPP-4i: dipeptidyl peptidase-4 inhibitors, MET: metformin, SU: sulfonylurea, TZD: thiazolidinedione.

Table 4. Reasons for changing first- and second-line therapies.

Reason for changing First Line Therapy	N = 271 (%)
Lack of Efficacy	229 (84.5%)
Hypoglycemic Event	16 (5.9%)
Weight Gain	48 (17.8%)
Side Effect	14 (5.2%)
Developed Acute Disease	1 (0.4%)
Developed Chronic Disease	2 (0.7%)
Affordability	1 (0.4%)
Inability to Self-Administer	0 (0.0%)
Patient Request	12 (4.4%)
Poor adherence	1 (0.4%)
Patient convenience	7 (2.6%)
Prescriber access reasons	0 (0.0%)
Drug interaction	0 (0.0%)
Physician preference	48 (17.7%)
Reason for Choosing a Second Line Therapy	
Efficacy	210 (77.5%)
Tolerability	102 (37.6%)
Weight	87 (32.1%)
Hypoglycemia	81 (29.9%)
Patient request	14 (5.2%)
Convenience	46 (17.0%)
Access Reason	3 (1.1%)
Cost	41 (15.1%)
Other	1 (0.4%)

Table 5. Concomitant medications.

	Total
Concomitant medications	n = 271
Concomitant Anti-hypertensive Drugs	119 (43.9%)
ACE inhibitors	93 (34.3%)
Beta-Blockers	37 (13.7%)
Calcium Channel Antagonists	23 (8.5%)
Diuretics	37 (13.7%)
Other Anti-hypertensive Drugs	3 (1.1%)
Concomitant Lipid-lowering Drugs	129 (47.6%)
High-Intensity statins	55 (20.3%)
Low Intensity Statins	68 (25.1%)
Fibrate	22 (8.1%)
Niacin	0 (0.0%)
Other Lipid-lowering Drugs	1 (0.4%)
Concomitant Antiplatelet drugs	66 (24.4%)
Aspirin	63 (23.2%)
Ticagrelor	0 (0.0%)
Prasugrel	0 (0.0%)
Clopidogrel	7 (2.6%)

4. Discussion

The DISCOVER study baseline report provided real-world observational data on patients' characteristics, management, and treatment patterns of patients T2DM in a country with an increasing incidence and prevalence of T2DM such as Jordan. The DISCOVER baseline data demonstrated that the patients with T2DM from Jordan were younger (mean age of 53.6 ± 11.3 vs. 57.5 ± 12 years) with a similar duration of diabetes (mean years of 5.98 ± 5.8 vs. 5.7 ± 5.3) and a higher BMI (mean kg/m^{2}of 30.8 ± 5.1 vs. 29.4 ± 6) compared to the entire cohort [7,8]. This study also revealed that there was a poor glycemic control after almost 6 years of diagnosis of diabetes in this patient population at the time of initiation of the second-line antidiabetic therapy. The reported

mean HbA1c level was 8.4% ± 1.6 among the cohort from Jordan which was more or less similar to the global average of 8.3% ± 1.7 for the entire DISCOVER study patient population of 14,668 from 37 countries [7]. The rate of the micro- and macrovascular complications was reported less in the Jordanian subgroup compared to the global population (10.3% and 12.5% vs. 19.4% and 14.7%, respectively) [7]. In the first-line treatment, the pattern globally was different in terms of higher use of metformin monotherapy (57.9%) and less use of the combination metformin/sulfonylureas (14.6%). For the second-line treatment, the combinations of metformin with either sulfonylureas (21.3%) or DPP-4i (25.1%) were the most commonly used in the overall population [7]. In addition, there was a small percentage (4.3%) of the patients who were on the combination of metformin and sodium-glucose-linked cotransporter type 2 (SGLT-2) inhibitors as a second-line treatment, which was not available at the time of initiating the study in Jordan.

This type of study is crucial to evaluate trends in diabetes management, and clinical outcomes, in order to identify opportunities to improve the standard of care in patients with T2DM. The delay in achieving glycemic and cardiovascular risk factors control needs to be investigated in this diverse clinical practice of endocrinologists and internists, representing both the public and private sectors. A more individualized and patient-centered approach, considering HbA1c target, patients' characteristics, and the presence of comorbidities, are recommended according the current clinical practice guidelines [8–10]. Achieving glycemic control, reducing LDL and blood pressure are important to reduce microvascular and macrovascular complications [11–15]. However, the baseline data in this study showed that there was a failure in treatment intensification in a timely manner which may have led to the overall poor control in this patient population. In Jordan, the initial antidiabetic treatment was mainly metformin-based therapy whether it was monotherapy in 46.9% of patients or in combination with sulfonylurea in 34.6%. In the second-line therapy, dual therapy of metformin and DPP-4i or triple therapy metformin, DPP-4i, and sulfonylurea or insulin-based therapy were the most commonly treatment prescribed. The drug treatment changes as a second-line therapy were in compliance with the some clinical guidelines [10,16–18], but not all [9]. The impact of these changes on glycemic control and diabetes-related complications will be evaluated over the 3-year follow-up period, especially with the increased utilization of the new class of antidiabetic drugs such as the SGLT-2 inhibitors.

5. Conclusions

The DISCOVER study is a comprehensive global program which provides valuable information about the real-world management of patients with T2DM in different clinical setting and countries. The baseline data for Jordan showed therapeutic inertia before the initiation of second-line therapy for patients with T2DM. A substantial number of patients were young and obese with multiple cardiovascular risk factors and poor glycemic control, requiring an earlier and more comprehensive management.

Acknowledgment

We would like to acknowledge Dr. Mazen Matalka from Advanced Healthcare Solutions for his help in writing the manuscript.

Author contributions

All authors contributed to the analysis and interpretation of the data, and critically reviewed all drafts. All authors approved the final draft for submission.

Disclosure statement

All authors have received payments from AstraZeneca as speakers, advisors and investigators.

Funding

This work has been supported by AstraZeneca.

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