Rate of Prescribing Statins for Primary Prevention of Atherosclerotic Cardiovascular Disease in Diabetic Patients

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ABSTRACT:

BACKGROUND:

Cardiovascular diseases are the major contributor to morbidity and mortality in patients with diabetes. Dyslipidemia, a common condition coexisting with type 2 diabetes, is a major cause of atherosclerosis and a risk factor for cardiovascular disease. Statin therapy plays an important role in the primary and secondary prevention of cardiovascular events in populations at elevated risk.

OBJECTIVE:

This study aims to examine the extent to which statins are used for primary prevention of atherosclerotic cardiovascular disease by diabetic patients, to identify gaps between guidelines and current daily practice, and to offer rational approach toward enhancing guideline adherence and improving quality of care.

MATERIALS AND METHOD:

A cross sectional study conducted from April 2019 to May 2020. Participants took part in a face to face personal interview in the outpatient clinic of Alsuwairah General Hospital. Patients included were those with type 1 or type 2 diabetes mellitus, aged 40-75 years, without a history of atherosclerotic cardiovascular disease.

RESULTS:

We included a total of 236 patients with diabetes mellitus, more than 2 thirds of them were ≥50 years of age. The majority (64.8%) were females. Patients with type 2 diabetes constitute 97.5% of the sample. Eighty six percent of patients have had diabetes for ≥2 years. Only 35 participants (14.8%) were on statin therapy. Among statin users, 62.9% have been doing so for less than 2 years. Use of statins was slightly more frequent in women than in men and it increases consistently with age; however, statistically non-significant. There was a significant association between statin prescription and increased duration of diabetes (P value 0.010).

CONCLUSION:

Statin prescription for primary prevention of ASCVD in diabetic patients is suboptimal. This finding underscores a major gap in addressing public health and cardiovascular disease burden in a population considered to be at high risk, and highlights an urgent need for optimising statin therapy and global risk factor control in diabetic patients without a known atherosclerotic cardiovascular disease.

KEY WORDS: Diabetes mellitus, Statin, Cardiovascular disease, Primary prevention.

INTRODUCTION:

Cardiovascular diseases cause 18 million deaths per year globally and a similar number of nonfatal cardiovascular events.[1] In patients with type 2 diabetes, cardiovascular disease is the major contributor to morbidity and mortality. [2] Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. [3] Dyslipidemia, a common condition coexisting with type 2 diabetes, is a major cause of atherosclerosis and a risk factor for cardiovascular disease (CVD).[4,5] Elevated low-density lipoprotein cholesterol (LDL-C) levels account for approximately half the population-attributable risk of myocardial infarction and approximately one quarter of the risk of ischemic stroke. [6]

Notably, dyslipidemia is common in Iraqi population. [7] The CVD-associated mortality rate in the Middle East is one of the highest in the world. In addition, studies such as the Gulf Registry of Acute Coronary Events (Gulf RACE) and the international case-control analysis of risk factors for a first myocardial infarction (INTERHEART) have found that patients in the Middle East who present with heart attacks are 10-12 years younger than those in Western countries. [8]

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Statin therapy plays an important role in the primary and secondary prevention of cardiovascular events in populations at elevated risk of atherosclerotic cardiovascular disease (ASCVD), [9] thus it is commonly used in subjects with diabetes. [10] The last 30 years have seen a large increase in the utilisation of statins, which is consistent with changes in recommendations in clinical guidelines. [11] Today, risk-reducing statin therapy is recommended for nearly all patients with diabetes 40 years of age or older, regardless of cholesterol level. [12] In 2005, the Joint British Societies (JBS) recommended that statins be offered to all people with diabetes to lower cholesterol, as the presence of diabetes alone was determined to identify high cardiovascular disease risk requiring appropriate management. Likewise, the national guidelines from the Scottish Intercollegiate Guidance Network (SIGN) recommends statin prescription in Type 2 diabetes more than 40 years irrespective of cholesterol level. [13]

The recently released American College of cardiology/American Heart Association guidelines changed the focus from treating to a target LDL cholesterol level to treating based on an individual's cardiovascular risk.[14] In Individuals with diabetes and LDL-C 70–189 mg/dL, moderate-intensity statin therapy should be initiated or continued for adults 40–75 years of age. [15] Whereas according to American diabetes association, moderate-intensity statin treatment should be considered for patients with diabetes aged 40–75 years, without additional ASCVD risk factors. [16]

On the other hand, the 2016 European Society of Cardiology/European Atherosclerosis Society guidelines for the management of dyslipidaemia state that in patients with type 2 diabetes and without CVD who are >40 years of age with one or more other CVD risk factors or markers of target organ damage, the recommended goal for LDL-C is <1.8 mmol/L (<70 mg/dL). While in all patients with type 2 diabetes and no additional risk factors and/or evidence of target organ damage, LDL-C <2.6 mmol/L (<100 mg/dL) is the primary goal. [17]

In the same fashion, National Institute for Health and Care Excellence 2014 guidelines on cardiovascular disease risk assessment and reduction, including lipid modification suggest offering atorvastatin 20 mg for the primary prevention of CVD to people with type 2 diabetes who have a 10% or greater 10-year risk of developing CVD estimated using the QRISK2 assessment tool. [18]

Despite large body of evidence and guidelines' recommendations, use of statins for the primary prevention of ASCVD in diabetic patients remains suboptimal. This study aims to examine the extent to which statins are used by diabetic patients aged 40-75 years, to identify gaps between guidelines and current daily practice, to offer rational approach toward enhancing guideline adherence, and to propose initiatives to improve quality of care.

MATERIALS AND METHOD:

A cross sectional study conducted from April 2019 to May 2020. Participants took part in a face to face personal interview in the outpatient clinic of Alsuwairah General Hospital. Patients included were those with type 1 or type 2 diabetes mellitus, aged 40-75 years, without a history of atherosclerotic cardiovascular disease (ASCVD). Atherosclerotic cardiovascular disease is defined as any history of angina, myocardial infarction (MI), coronary angiography, coronary artery bypass surgery (CABG), stroke, transient ischemic attack, or peripheral arterial disease. Using a structured case form, patients were inquired about their ages, duration of diabetes, adherence to diabetic diet, pattern and adherence to antidiabetic therapy, and use of statins. Diagnosis of diabetes is based on a history of fasting blood sugar ≥ 126 mg/dl or random blood sugar ≥ 200 mg/dl on two occasions. Type of diabetes is determined according to the age at onset and pattern of treatment.

A total of 259 case forms were completed; after arranging them in an alphabetic order, 15 forms were found to be filled for individuals who have already participated in the study and were excluded. Furthermore, 8 case forms with missing data for one or more variables were excluded. Finally, data of 236 patients were processed statistically.

Statistical analysis

Data were entered, managed and analysed using the Statistical Package for Social Sciences (SPSS) version 26. Descriptive statistics of variables were presented as frequencies and proportions. Chi square test was used to assess the significance of association between statin use and other variables. Fisher's exact test was used as an alternative when Chi square was inapplicable. Level of significance was set at 0.05 (two tailed P value ≤ 0.05).

RESULTS:

This study enrolled a total of 236 patients with diabetes mellitus aged 40-75 years. The majority, 153 (64.8%), were females. Patients with type 2 diabetes constitute 97.5% of the sample.

The vast majority of patients have had diabetes for ≥2 years and more than half of them for ≥5 years. Of the study cohort, only 20 participants (8.5%) were adherent to diabetic diet. Baseline demographic and clinical characteristics are given in Table 1.

Overall, 15 individuals were taking no antidiabetic agent. In patients with type 2 diabetes, a combination of metformin and sulphonylurea was used by 28.7%, while insulin therapy alone was received by 17.4%. The combination of insulin and oral antidiabetic agents was used by only 2 patients (0.9%) among this subgroup. Of the subgroup of patients receiving antidiabetic drugs, 131 (59%) were adherent to treatment. Figure 1 shows the number of people taking antidiabetic drugs and compliance with treatment. Table 2 presents the patterns of antidiabetic therapy.

In the overall cohort, the vast majority of patients was not using statins. Only 35 participants (14.8%) were on statin therapy (Figure 2). Among statin users, 22 patients (62.9%) have been doing so for less than 2 years. Seven patients (3%) reported previous use of a statin which had been discontinued for different reasons. Table 3 summarises current and previous statin therapy.

Although statistically non-significant, use of statins was slightly higher in women than in men, 16.3% versus 12% respectively. Moreover, the likelihood of being on a statin consistently increases with age, 18.1% in the age category of ≥60 years compared to 15.3% and 10.3% in the age categories of 50-59 years and 40-49 years respectively . There was a significant association between statin prescription and increased duration of diabetes (P value 0.010). The relationships between statin prescription and demographic and clinical characteristics of the study population are provided in Table 4.

Table1: Baseline demographic and clinical characteristics of the study population.

Variable		Frequency (N=236)	Percentage (%)
Gender	Male	83	35.2
	Female	153	64.8
Age (years)	40 - 49	68	28.8
	50 - 59	85	36.0
	≥ 60	83	35.2
Type of diabetes	Type 1	6	2.5
	Type 2	230	97.5
Duration of diabetes (years)	< 2	32	13.5
	2 to less than 5	63	26.7
	5 to less than 10	71	30.1
	10 to less than 20	58	24.6
	≥ 20	12	5.1
Dietary adherence	Yes	20	8.5
	No	216	91.5

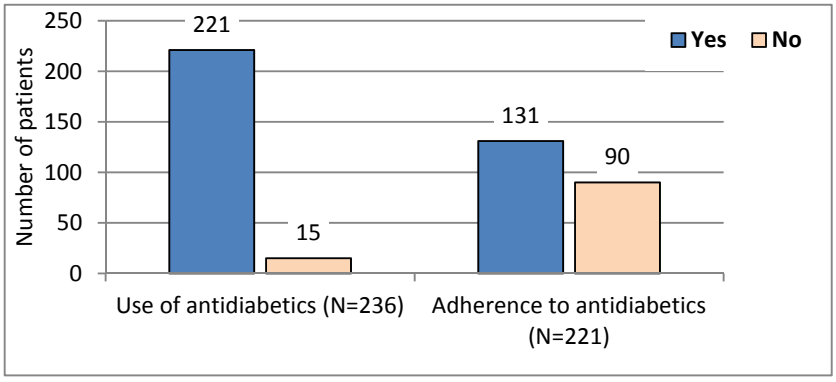

Figure 1: Number of patients using antidiabetic agents and their adherence to treatment.

Table 2: Patterns of antidiabetic therapy received by subgroup of patients with type 2 diabetes.

Variable	Frequency (N=230)	Percentage (%)
Metformin and Sulphonylurea	66	28.7
Sulphonylurea	57	24.8
Insulin	40	17.4
Metformin	24	10.4
Metformin and Gliptin	16	7.0
Metformin, Sulphonylurea and Gliptin	4	1.7
Insulin and oral anti-diabetics	2	0.9
SGLT 2 inhibitor*	1	0.4
Not certain**	5	2.2
No antidiabetics	15	6.5

* Sodium glucose cotransporter 2 inhibitor.
**Not certain: The patient does not know exactly what type of oral antidiabetic agent(s) they are taking.

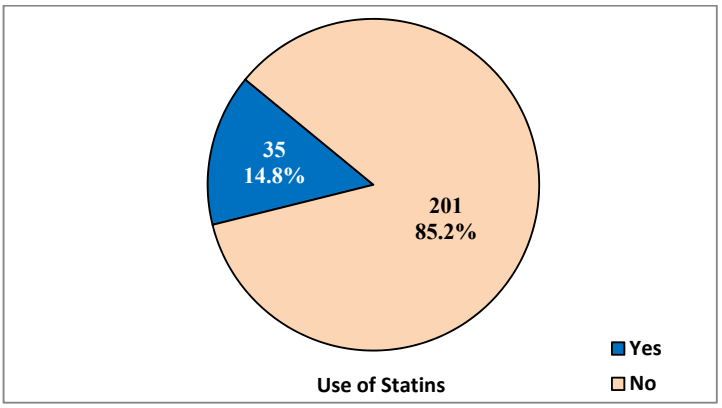

Figure 2 :Distribution of statin use among the study population.

Table 3: Duration of current statin therapy and history of previous use of a statin.

Variable		Number of patients	Percentage (%)
Duration of current statin therapy	Less than 2 years	22	62.9
	2 – 5 years	9	25.7
	More than 5 years	3	8.6
	Not certain*	1	2.8
Total		35	100
Previous statin use	Yes	7	3.0
	No	229	97.0
Total		236	100
Reasons to discontinue	Compliance related issues	5	71.4
	Cost related issues	1	14.3
	Falsely discontinued**	1	14.3
Total		7	100

*Patient does not know exactly how long he/she has been on statin therapy.
**Falsely discontinued by a physician.

Table 4: Associations between statin prescription and demographic and clinical characteristics of the study population.

Variable		Statin prescription				P. value
		Yes (N=35)		No (N=201)		
		Frequency	%	Frequency	%	
Gender	Male	10	12.0	73	88.0	0.376
	Female	25	16.3	128	83.7	
Age (years)	40 – 49	7	10.3	61	89.7	0.404
	50 – 59	13	15.3	72	84.7	
	≥ 60	15	18.1	68	81.9	
Type of diabetes	Type 1	2	33.3	4	66.7	0.218
	Type 2	33	14.3	197	85.7	
Duration (years)	Less than 2	2	6.2	30	93.8	**0.010**
	2 to less than 5	6	9.5	57	90.5	
	5 to less than 10	10	14.1	61	85.9	
	10 to less than 20	11	19.0	47	81.0	
	≥ 20	6	50.0	6	50.0	
Dietary adherence	Yes	5	25.0	15	75.0	0.190
	No	30	13.9	186	86.1	
Use of anti-diabetics	Yes	35	15.8	186	84.2	0.136
	No	0	0.0	15	100.0	
Type of anti-diabetic therapy	Metformin and Sulphonylurea	15	22.7	51	77.3	0.067
	Sulphonylurea	4	7.0	53	93.0	
	Insulin	10	21.7	36	78.3	
	Metformin	3	12.5	21	87.5	
	Metformin and Gliptin	1	6.2	15	93.8	
	Metformin, Sulphonylurea and Gliptin	1	25.0	3	75.0	
	Insulin and oral anti-diabetics	1	50.0	1	50.0	
	SGLT 2 inhibitor*	0	0.0	1	100.0	
	Not certain**	0	0.0	5	100.0	
	No antidiabetics	0	0.0	15	100.0	
Adherence to anti-diabetic drugs***	Yes	20	15.3	111	84.7	0.850
	No	15	16.7	75	83.3	
Previous statin use	Yes	0	0.0	7	100.0	0.598
	No	35	15.3	194	84.7	

*Sodium glucose cotransporter 2 inhibitor.
**The patient does not know exactly what type of oral antidiabetic agent(s) they are taking.
***Subgroup of patients on antidiabetic agents.

DISCUSSION:

This study examined the rate of statin prescription for primary prevention of ASCVD in patients with diabetes. Although all people participated in this study were eligible for statin treatment based on contemporary guidelines, only 14.8% are currently on a statin. Statin prescription was significantly associated with increasing duration of diabetes.

Iraq is facing an epidemic of diabetes mellitus, the prevalence of diabetes increased from 5% in 1978 to 19.7% in 2012. [19] A cross-sectional study conducted at Al-Faiha Diabetes, Endocrine and Metabolism Center in Basrah (southern Iraq); found that among adults with type 2 diabetes mellitus, there is an increased frequency of cardiovascular disease and its modifiable risk factors. In addition, the majority of these patients had lipid profiles outside the target range. [20]

Stain is commonly used in subjects with diabetes for both primary and secondary prevention of cardiovascular diseases. Multiple clinical trials have demonstrated the beneficial effects of statin therapy on ASCVD outcomes in subject with and without coronary heart disease (CHD). Subgroup analyses of patients with diabetes in larger trials and trials in patients with diabetes showed significant primary and secondary prevention of ASCVD events and CHD death. [16] Large-scale evidence from randomised trials shows that statin therapy reduces the risk of major vascular events (i.e., coronary deaths or myocardial infarctions, strokes, and coronary revascularization procedures) by about one-quarter for each 1 mmol/L reduction in LDL cholesterol during each year (after the first) that it continues to be taken**.** [21] Moreover, in Collaborative Atorvastatin Diabetes Study (CARDS), Colhoun *et al* concluded that atorvastatin 10 mg daily is safe and efficacious in reducing the risk of first cardiovascular disease events, including stroke, in patients with type 2 diabetes without high LDL-cholesterol. [22]

Furthermore, there was also no evidence of heterogeneity of effect in subgroups defined according to sex, age, and race or ethnic group. Treatment with rosuvastatin at a dose of 10 mg per day resulted in a significantly lower risk of cardiovascular events than placebo in an intermediate-risk, ethnically diverse population without cardiovascular disease. [6]

Statins not only reduce LDL-C but halt progression, and may contribute to regression of coronary atherosclerosis. [23] In JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), which included apparently healthy men and women who did not have hyperlipidemia but did have elevated levels of high sensitivity C-reactive protein, the rates of a first major cardiovascular event and death from any cause were significantly reduced among the participants who received rosuvastatin as compared with those who received placebo. [24]

According to the European Society of Cardiology/European Atherosclerosis Society guidelines, patients with type 2 diabetes or type 1 diabetes with target organ damage (such as microalbuminuria) are classified as very high-risk group. It has been shown that primary prevention with statins is likely to be cost saving if prescribed to high-risk patients, at least as much as (and probably more than) primary prevention with anti-hypertensives or aspirin. [25] These findings were also confirmed by observational retrospective studies. [26,27] Consequently, most guidelines state that statin therapy should be initiated and maintained for the primary prevention of CVD in diabetic patients aged ≥40 years.

We found obvious deficit in care regarding guideline recommended statin therapy for diabetes mellitus. Suboptimal use of statins was noted in other studies all over the world. In a study conducted in Ethiopia, statins were prescribed for primary prevention of ASCVD in 55.7% of patients with type 2 diabetes aged 40-75 years. [28] Statins were prescribed in 55% of diabetic patients in an Indian multisite registry-based study. [29] Two Malaysian studies involved people with type 2 diabetes aged between 40 to 75 years; one recruited patients from the medical wards of two tertiary hospitals and the other enrolled individuals in the endocrinology clinic, showed that 65 % and 81.1% had a statin therapy prescription respectively.[30,31] Likewise, a study conducted in Denmark revealed that 53% of diabetic patients was not using statins before their first MI. [12]

In Australia, a cross sectional representative study revealed that only 32.5% of patients with high absolute risk receive statins for primary prevention of CVD. [32] Similar findings were confirmed in the French MONA LISA study, in which the vast majority (72%) of those eligible for primary prevention (high-risk group with multiple co-morbidities but no CVD) is excluded from the recommended therapy.[25] The proportion of diabetic patients taking antidyslipidaemic medications in Korea was as low as 19.1%. [4] Steen *et al* found that only 40% of patients with only DM had evidence of a filled statin prescription. [33] Another American study

showed that only 52% of patients with diabetes older than 40 years were using statins, the authors suggest that the most likely explanation is an overreliance on hyperlipidaemia instead of cardiovascular risk when deciding whether to prescribe a statin. [14] Similarly, a cross sectional analysis of the baseline data from The Irish Longitudinal Study on Ageing found that the proportion taking statins for primary prevention in those with known diabetes was 57.4%. [23] Low rates of prescription was also confirmed in China. After a median follow-up of 4.9 years, Ting *et al* found that only 23% of patients with type 2 diabetes were prescribed statins. [34] Whereas in Scotland, only 68% of men and 69% of women overall had a record of statin prescription in the 2 years following diagnosis with diabetes. [13] Finally, a cross-sectional study from 19 general practices in the UK showed that of patients eligible for statin therapy, 80% were prescribed medication. Statin prescription was more common in younger patients and in females. [35]

Noncompliance with best practice in diabetes is common. [36] However, our data do not explain why so many diabetic patients at very high cardiovascular risk are not treated with statins. In Middle East, general lack of awareness and lack of adherence to lipid guidelines by physicians result in a wide gap between guidelines and current daily practice in the management of dyslipidaemia. [8] Furthermore, a low rate of statin prescription was also reported in hypertensive patients with dyslipidaemia, a study conducted in Tikrit-Iraq revealed that only 22.1% were on statin therapy. [37]

Although most physicians support the guidelines use, only half of them use them and in average their knowledge of guidelines is not satisfactory. [38] Most clinicians can barely keep pace with the rapid advances in pharmacotherapy.[39] Physician's adherence is critical in translating recommendations into improved outcomes. However, a variety of barriers undermine this process. Lack of awareness and lack of familiarity affect physician's knowledge of a guideline. Self-efficacy, outcome expectancy, and the inertia of previous practice are also potential barriers. In addition, external barriers such as lack of time and resources and organizational constraints can affect a physician's ability to execute recommendations. [40, 41]

A less common scenario that may affect prescribing adherence to guidelines is the presence of concerns or disagreement with the final recommendations or the way by which the guidelines were formulated. [2] Importantly, perceived medication risk may affect prescribing patterns. [42] However, it has been argued that the harmful effects of statin therapy can usually be reversed without residual effect by stopping the statin, whereas 'harmful effects of heart attacks or strokes that occur because statin therapy has not been used can be devastating'.[11] On the other hand, patient's preference and willingness to accept lifelong medications in the absence of an overt disease had a role to play in the low level of statin use for primary prevention.[23] Retrospective database analyses have revealed that 50% of patients receiving statins discontinue therapy after 1 year of treatment. [25] Lastly, Fürthauer and colleagues found that the most frequent reason for physicians to deviate from guideline recommendations was that they falsely assumed that a certain prescription was not indicated or necessary. [43]

To our knowledge, this is the first Iraqi study on the primary prevention of ASCVD in diabetic patients. It also assesses patterns of treatment of diabetes and dietary and drug adherence. Our study has some limitations; we only considered factors in connection with diabetes and its treatment, and did not investigate statin prescription in relation to other cardiovascular risk factors like hypertension and smoking. Because of absence of medical records, our study identifies medical conditions and prescription data by self-report of the patients. Additionally, it does not include laboratory values such as lipid levels, and was conducted in one centre.

CONCLUSION:

Statin prescription for primary prevention of ASCVD in diabetic patients is suboptimal. This finding underscores a major gap in addressing public health and cardiovascular disease burden in a population considered to be at high risk, and highlights an urgent need for optimising statin therapy and global risk factor control in diabetic patients without a known atherosclerotic cardiovascular disease. Strategies to optimise prescriptions are better clinicians' awareness of guidelines and continuing medical education to improve quality of preventive care, together with regular treatment reviews in all patients. Researches into effective strategies to improve physician adherence to CVD prevention guidelines are merited.

Acknowledgement

The authors thank all medical and nursing staff of outpatient clinic in Alsuwairah General Hospital for their kind help and support in facilitating this study.

Competing interests

The authors declare that they have no competing interests.

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