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PREVALENCE AND EFFICACY OF STATIN THERAPY AMONG TYPE 2 DIABETIC PATIENTS

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ABSTRACT

Background: The American College of Cardiology (ACC) and American Heart association (AHA) standards of care for diabetes documented that statin therapy should be initiated in all diabetic patients for primary and secondary prevention of cardio-vascular diseases. **Objectives:** To investigate the adherence of type 2 diabetic patients to the recommendations of the American College of Cardiology (ACC) and American Heart association (AHA) regarding Statin treatment as well as the impact of statins on glycemic control. **Subjects and methods:** A nested case-control study was conducted among adult diabetic type 2 patients aged 18 years or more attending chronic disease clinic (CDC), Department of Family Medicine, King Fahd Armed Forces hospital, Jeddah, Saudi Arabia during the study period (December, 2015-January, 2016). Then they were classified into two groups. Those having statin treatment were considered as cases whereas those not treated with statin were considered as controls. A short specific form was completed by the treating physician for each patient. It addressed demographic variables. Clinical data were abstracted from the patients' record. **Results:** The study included 285 type 2 diabetic patients. Female to male ration was 1:1.22. The prevalence of statin therapy was 75.8%. Patients with longer duration of the disease (>10 years) tended to use statin compared to those with shorter duration (<1 year) (90.6% versus 36.7%), p<0.001. Patients with complications were more likely to use statin opposed to those without complications (88.4% versus 67.6%), p<0.001. Patients treated with combined therapy (insulin and oral hypoglycemic) were more likely to use statin than those treated with diet only (94.7% versus 23.5%), p<0.001. Patients who always compliant with diabetic regimen were less likely to use statin compared to those who never compliant with diabetic regimen (60% versus 79.4%), p=0.010. Patients with history of chronic diseases were more likely to use statin compared to those without such history (87.1% versus 44.7%), p<0.001. Dissatisfaction with diabetic therapy was significantly associated with the use of statin, p<0.001. Fasting blood glucose is significantly higher among patients treated with statin compared to those not treated with statin (144.15±58.56 versus 123.30±61.08, p=0.011). Also, the glycated hemoglobin level was higher among patients treated with statin than those not treated with it (10.12±10.83 versus 8.91±7.77). However, the difference was not statistically significant. **Conclusion:** Statin use is associated with increased fasting blood glucose and HbA1c levels among patients with type 2 diabetes. As the evidence for statin therapy in reducing mortality is much stronger than the evidence to support glucose lowering therapy, clinicians managing patients with diabetes on statins should not stop statin use but ensure that hyperglycaemia is kept under control.

KEYWORDS: Statins; glycated hemoglobin; Fasting blood glucose; type 2 diabetes.

INTRODUCTION

The American College of Cardiology (ACC) and American Heart association (AHA) standards of care for diabetes documented that statin therapy should be initiated in all diabetic patients for primary and secondary prevention of cardio-vascular diseases.[1]

Currently there are two well-known studies with good evidence to support the role of statins in primary prevention for the diabetic population. These are CARDS and HPS.[2, 3] They included diabetic patients with other CHD risk factors and still showed benefit within this subgroup.

The benefit of lowering of cholesterol with statins is well documented for primary and secondary prevention of CHD in non-diabetics with both high and relatively 'normal' serum cholesterol levels.[4-8] The role played by statins in secondary prevention of CHD among diabetics has also been proved in three key studies (4S, CARE, LIPID).[9-11] Statins have some other effects other than lowering cholesterol, including anti-inflammatory actions. With existing evidence supporting the role of inflammation in atherosclerosis, this may prove to be an important consideration. However, the benefits of statins

seem to be related to the degree of cholesterol lowering.[12]

The high incidence of CHD in diabetic patients has led many to think that diabetes should be considered as a CHD risk equivalent and therefore all diabetic patients should be given a statin. Haffner et al,[13] reported that the incidence of CHD events in Finland was high equally in patients with diabetes and in non-diabetic patients with previous myocardial infarction. Also, in a study by Evans et al, the event rate in people with diabetes without CHD, was much higher than in non-diabetic people without CHD but this was not as high as in the event rate in non-diabetic subjects with previous myocardial infarction.[14] This findings raise the question - should simply all people with diabetes be treated with statin therapy?

On the other hand, there are some reasons why treating all diabetic patients with statins is not applicable.[15] The cost burden of treating all diabetic patients with statins from the onset of diagnosis of diabetes would be considerable, given the global rapid increase in the incidence of type 2 diabetes. The incidence of type 2 diabetes is also increasing within younger groups. Although the relative risk of coronary heart diseases is high compared in diabetic younger groups compared to age-matched non-diabetic subjects, the absolute incidence of CHD in younger diabetic groups is relatively low and the short-term benefits of treating them with statins would be less.[16]

This study was carried out to investigate the adherence of type 2 diabetic patients to the recommendations of the American College of Cardiology (ACC) and American Heart association (AHA) regarding Statin treatment as well as the impact of statins on glycemic control.

SUBJECTS AND METHODS

A nested case-control study was conducted among adult diabetic type 2 patients aged 18 years or more attending chronic disease clinic (CDC), Department of Family Medicine, King Fahd Armed Forces hospital, Jeddah, Saudi Arabia. during the study period (December, 2015-January, 2016). Then they were classified into two groups. Those having statin treatment were considered as cases whereas those not treated with statin were considered as controls.

The sample size was calculated by Epi info, version 7 assuming that the approximate number of adult, diabetic type 2 patients attending CDC per two months as1000, expected frequency of using statin: 50%, accepted margin of error: 5% and confidence level as 95%. The estimated minimum sample size was 278 diabetic patients.

The estimated number of adult diabetic patients seen per day is 24 at CDC, department of Family Medicine, King Fahd Armed Forces hospital, Jeddah, KSA. A systematic random sampling technique was adopted (every second patient was selected), so an average of 12 patients were invited to participate in the study daily and 60 patients weekly. Consequently, a total of 26 working days were needed to collect information from the estimated sample size.

A short specific form developed by the researcher was completed by the treating physician for each patient. It addressed demographic variables such as gender, age and level of education In addition to the number and nature of chronic medical conditions. Clinical data were abstracted from the patients' record and included duration of diabetes, co-morbidities, fasting or random capillary blood glucose measurements, last hemoglobin (Hgb) Alc measurements, treatment modality (i.e., oral agents/insulin), and recent hospital admissions due to diabetes.

Necessary approval by local Research and Ethics Committee was obtained prior to the study.

Data were analyzed using SPSS software, version 22. Frequency and percentage were used to describe categorical variables whereas arithmetic mean and standard deviation were used to describe continuous variables. Chi-square and student`s t-tests were used to compare cases and controls. A significant level was determined at $p<0.05$.

RESULTS

The study included 285 type 2 diabetic patients. Female to male ration was 1:1.22. The prevalence of statin therapy was 75.8% as illustrated from figure 1. Table 1presents the comparison between diabetic patients treated with statin and those not treated with it regarding socio-demographic characteristics. Older patients (>60 years) were more likely to use statin compared to younger patients (20-30 years) (88.9% versus 13.3%), $p<0.001$. Similarly, ever married patients were more likely to use statin compared to singles, $p<0.001$. Lower educated patients (illiterate and primary educated) were more likely to use statin compared to university graduated patients (85.6% and 82.8% versus 53%), $p<0.001$. Patients gender was not a significant predictor for statin use.

Regarding diabetes-specific characteristics, patients with longer duration of the disease (>10 years) tended to use statin compared to those with shorter duration (<1 year) (90.6% versus 36.7%), $p<0.001$. Patients with complications were more likely to use statin opposed to those without complications (88.4% versus 67.6%), $p<0.001$. Patients treated with combined therapy (insulin and oral hypoglycemic) were more likely to use statin than those treated with diet only (94.7% versus 23.5%), $p<0.001$. Patients who always compliant with diabetic regimen were less likely to use statin compared to those who never compliant with diabetic regimen (60% versus 79.4%), $p=0.010$. Patients with history of chronic

diseases were more likely to use statin compared to those without such history (87.1% versus 44.7%), p<0.001. Dissatisfaction with diabetic therapy was significantly associated with the use of statin, p<0.001.

As seen in table 3, fasting blood glucose is significantly higher among patients treated with statin compared to those not treated with statin (144.15±58.56 versus 123.30±61.08, p=0.011). Also, the glycated hemoglobin level was higher among patients treated with statin than those not treated with it (10.12±10.83 versus 8.91±7.77). However, the difference was not statistically significant.

Table 1: comparison of socio-demographic characteristics between type 2 diabetic patients treated with statin and those not treated with it.

	Cases N=216 N (%)	Controls N=69 N (%)	p-value
Age (years)			
20-30 (n=15)	2 (13.3)	13 (86.7)	<0.001
31-40 (n=33)	12 (36.4)	21 (63.6)	
41-50 (n=86)	68 (79.1)	18 (20.9)	
51-60 (n=106)	94 (88.7)	12 (11.3)	
>60 (n=45)	40 (88.9)	5 (11.1)	
Gender			
Male (n=128)	101 (78.9)	27 (21.1)	0.267
Female (n=157)	115 (73.2)	42 (26.8)	
Marital status			
Married (n=215)	164 (76.3)	51 (23.7)	<0.001
Single (n=10)	2 (20.0)	8 (80.0)	
Widowed (n=49)	41 (83.7)	8 (16.3)	
Divorced (n=11)	9 (81.8)	2 (18.2)	
Educational level			
Illiterate (n=125)	107 (85.6)	18 (14.4)	<0.001
Primary (n=29)	24 (82.8)	5 (17.2)	
Intermediate (n=29)	21 (72.4)	8 (27.6)	
Secondary (n=35)	28 (80.0)	7 (20.0)	
University (n=66)	35 (53.0)	31 (47.0)	

Table 2: comparison of medical characteristics between type 2 diabetic patients treated with statin and those not treated with it.

	Cases N=216 N (%)	Controls N=69 N (%)	p-value
Diabetes duration (years)			
<1 (n=30)	11 (36.7)	19 (63.3)	<0.001
>1-<5 (n=86)	54 (62.8)	32 (37.2)	
>5-10 (n=105)	93 (88.6)	12 (11.4)	
>10 (n=64)	58 (90.6)	6 (9.4)	
Diabetic complications			
No (n=173)	117 (67.6)	56 (32.4)	<0.001
Yes (n=112)	99 (88.4)	13 (11.6)	
Hospitalization due to DM			
No (n=256)	194 (74.6)	65 (25.4)	0.167
Yes (n=29)	25 (86.2)	4 (13.8)	
Diabetic therapy			
Diet (n=34)	8 (23.5)	26 (76.5)	<0.001
Oral hypoglycemic (n=118)	88 (74.6)	30 (25.4)	
Insulin (n=58)	49 (84.5)	9 (15.5)	
Combined therapy (n=75)	71 (94.7)	4 (5.3)	
Satisfaction with diabetic therapy			
Very satisfied (n=35)	19 (54.3)	16 (45.7)	<0.001
Somewhat satisfied (n=135)	95 (70.4)	40 (29.6)	
Neutral (n=106)	96 (90.6)	10 (9.4)	
Somewhat dissatisfied (n=5)	4 (80.0)	1 (20.0)	

Very dissatisfied (n=4)	2 (50.0)	2 (50.0)	
Compliance with diabetic regimen Always (n=55) Sometimes (n=196) Never (n=34)	 33 (60.0) 156 (79.6) 27 (79.4)	 22 (40.0) 40 (20.4) 7 (20.6)	0.010
History of chronic diseases No (n=76) Yes (209)	 34 (44.7) 182 (87.1)	 42 (55.3) 27 (12.9)	<0.001

Table 3: Comparison of fasting blood glucose and glycated hemoglobin between type 2 diabetic patients treated with statin and those not treated with it.

	Cases N=216 Mean±SD	Controls N=69 Mean±SD	p-value
Fasting blood glucose (mg/dl)	144.15±58.56	123.30±61.08	0.011
Glycated hemoglobin (%)	10.12±10.83	8.91±7.77	0.392

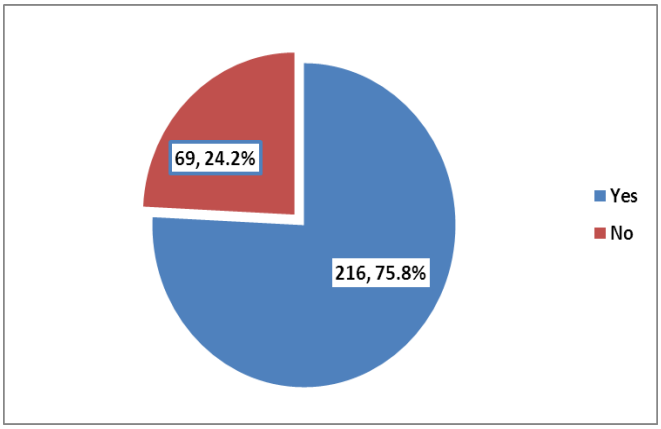

Figure 1: prevalence of using statin among type 2 diabetic patients attending the chronic disease clinic (CDC), King Fahd Armed Forces hospital, Jeddah, Saudi Arabia.

DISCUSSION

The current study revealed two important key findings. First, patients with type 2 diabetes who used statins have significantly higher fasting blood glucose compared those not using statins. Second, although not significant, poorer glycemic control, reflected by HbA1c levels more reported among those using statins compared to those not using statins. Recently, Liew et al reported that patients with diabetes who used statins have significantly higher HbA1c levels compared to those not using statins.[17] Higher HbA1c levels in statin users suggests that statins affect glycaemic control. Poor glycaemic control with statin use could increase cardiovascular risk in the long-term in patients on statins. Therefore regular monitoring of glycaemic control is important in this group of patients.

Kostapanos et al (2010) investigated the effect of statins drugs on glycemic outcomes in order to identify types of statins which may be preferentially used to improve glycemic control. They concluded that from all statins, pravastatin proved to beneficially affect glucose metabolism and consequently decrease the risk of diabetes. Controversial findings have been reported with other statins commonly prescribed in the clinical setting (rosuvastatin, atorvastatin and simvastatin).[18]

In addition, the US Federal and Drug Administration in February 2012 revised statin drug labels and include the information that increases in fasting blood glucose and glycated haemoglobin levels have been reported with the use of statins.[19] Their warnings were based on evidence from meta-analysis and cohort studies[20-22] as well as two controlled trials,[23, 24] as Statin therapy was found to be associated with worsening glycaemic control.

Fasting blood glucose level was significantly higher in patients with diabetes who were on statins. The same has been reported by Liew et al.[17] A significantly greater proportions of diabetics on statins were reported diabetic medications (oral hypoglycemic and/or insulin) compared with diabetics not on statins. It is a possibility that poorer glycaemic control in the diabetics on statin group necessitates the use of medication for improving fasting blood glucose control.

Diabetes duration could potentially affect glycaemic control. In the current study, longer diabetes duration was significantly associated with statin use in patients with diabetes.

Most of the previous studies which have shown similar findings were conducted in clinical trial participants, which had strict controlled settings. Our study design could only show association and not causation. It is possible that the association seen between statins and hyperglycaemia may be due to the clustering of hyperlipidaemia, hypertension and glucose intolerance, which are known features of metabolic syndrome. However, it has highlighted that statin is associated with poorer glycaemic control in patients with diabetes in a 'real-life' setting.

Statins have been shown to affect glucose metabolism in multiple ways such as by inhibition of insulin secretion and downregulation of a glucose transporter in adipocytes.[25] Clinicians managing patients with diabetes should take note of this and ensure that glycaemic control is managed accordingly.

Among important limitations of this study, its basic design which limits the causality relationship between studied factors and the outcome. Second, the cases and controls were not matched regarding important factors that could affect the glycemic control such as age and disease-specific characteristics. Therefore, further age and disease-status matching cohort study is recommended to better investigate the impact of statin therapy on glycemic control.

Conclusively, statin use is associated with increased fasting blood glucose and HbA1c levels among patients with type 2 diabetes. As the evidence for statin therapy in reducing mortality is much stronger than the evidence to support glucose lowering therapy, clinicians managing patients with diabetes on statins should not stop statin use but ensure that hyperglycaemia is kept under control.

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