FREQUENCY OF STATIN USE IN TYPE 2 DIABETICS HAVING MACROVASCULAR DISEASE- AT A TERTIARY CARE HOSPITAL OF KARACHI

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Background: During the last two decades with the introduction of statins large reductions in cholesterol concentrations were easily and safely achievable and this led to studies that demonstrated benefits of statin use. But only fewer than one fourth of adults with coronary heart disease were receiving lipid-lowering drugs in a cross sectional health survey done in England. Thus this study was designed to evaluate the frequency of statin use in type 2 Pakistani diabetic subjects with macrovascular disease attending a tertiary care unit in Karachi, Pakistan. **Methods:** Records of type 2 diabetic subjects coming to the outpatient department of Baqai Institute of Diabetology and Endocrinology from September 1996 to December 2001 was analyzed for their anthropometric and biochemical characteristics. Patients having any macrovascular disease were identified and frequency of statin use by these subjects was studied. **Results:** Out of a total of 2152 patients 502 (252 males, 250 females) having macrovascular disease were identified. Only 16.5% of them (44 males, 39 females) were taking statins. Use of statins was higher amongst those who had angina (20%) or myocardial infarction (17%) compared to those who had stroke (10%). Sixty two percent of the users while 52% of the non-users had elevated blood cholesterol. **Conclusion:** Frequency of statin use in the subjects studied was much lower than was warranted with respect to their disease status. Presence of elevated blood cholesterol despite using statins suggested inappropriate treatment in these subjects. Further studies are required to identify the factors leading to low use of statins in type 2 diabetic subjects with macrovascular symptoms.

Keywords: Statin Users, Frequency, Lipid profile, Type 2 Diabetes, Pakistan, Macrovascular, Angina, Myocardial Infarction, Stroke.

INTRODUCTION

Diabetic dyslipidemias are related to cardiovascular disorders and also associated with the macrovascular complications of diabetes. Macrovascular complications are among the chief causes of major morbidity and mortality in people with diabetes [1-2]. Diabetes has 3-5 times higher absolute risk of coronary heart disease (CHD) death at each level of blood cholesterol than non-diabetic subjects [3].

In the last 20 years studies have indicated that smoking cessation, beta blockers, anti-platelet agents, ACE-inhibitors and lipid lowering agents, each reduce the risk of vascular events to a moderate but important degree [4-7]. With the introduction of statins large reductions in cholesterol concentrations were easily and safely achievable and this finding led to a series of studies that demonstrated benefits in selected populations.

Several large studies such as 4S[8], CARE[9] and LIPID[10] have provided evidence for effectiveness of lipid-lowering drugs in macrovascular disorders; and have proven that lowering Low Density Lipoproteins (LDL) with statins reduces the risk of CHD mortality and morbidity in high risk patients by a quarter to half. The CHD risk

was higher among the subjects with diabetes than those without it, hence the absolute benefits of statins appears to be larger in diabetics. The ATP-III report by the National Cholesterol Education Program (NCEP) lists high LDL levels to be the major cause of CHD and diabetes is taken as CHD risk equivalent [11]. United Kingdom Prospective Diabetes Study (UKPDS) has also shown direct association of CHD risk with LDL levels among 3000 type 2 diabetic subjects and inverse association with HDL Cholesterol [12].

Heart Protection Study (HPS) has also clearly shown that lowering lipid levels with a statin is of value in much broader populations than currently realized and all patients with vascular disease or having CHD risk would benefit from statinsincluding those who were poorly represented in other studies such as elderly (>75 years of age), women, having LDL < 96 mg/dl, diabetics with no CHD and patients having stroke or peripheral vascular disease [13].

Thus it is universally recommended that statins should be prescribed to all patients with coronary heart disease [14]. Patients with myocardial infarction (MI) are recommended to use statins if their total cholesterol was $\geq$ 180 mg/dl and patients with angina should use statins if total cholesterol $\geq$ 200 mg/dl [15].

Though prescription of statins has increased in recent years, it is still well below the recommended level in the treatment of patients with coronary disease in UK. In a cross sectional analysis of data from health survey of England, only 19.9% of adults with coronary heart disease were receiving lipid-lowering drugs [15]. There has not been any such assessment of adequacy of use of lipid lowering drugs in our country.

The purpose of this study was to assess the type 2 diabetics with macrovascular disease attending a tertiary care unit in Karachi.

MATERIAL AND METHODS

Baqai Institute of Diabetology and Endocrinology (BIDE) is a tertiary care hospital providing specialist care to the diabetic population. ince its inception the institute maintains computerized records of diabetic patients. For this study computerized records of the first visit of all type 2 diabetic subjects older than 18 years of age to the outpatient department of Baqai Institute of Diabetology and Endocrinology from September 1996 to December 2001 was analyzed for their anthropometric and biochemical characteristics. The information to be retrieved included computer code, age, sex, occupation, place of residence, marital status, family history, smoking, year of diagnosis of diabetes and medications already being taken. Therefore, minimal confidentiality or ethical issues were involved. Furthermore names were not disclosed anywhere and the researchers used only the computer code for identification purposes.

Out of the total 2152 patients 502 subjects having any macrovascular disease were identified and frequency of statin use by these patients was studied.

Glycemic control was assessed by fasting plasma glucose and HbA1c.

Venous plasma glucose was estimated by GOD-PAP Method[16]. HbA1c was assessed by DiaSTAT Hemoglobin A1c Program, Bio-Rad[17]. HbA1c, was used as the basic indicator of glycemic control. Values of < 7%, 7 - 8.5% and > 8.5% indicated good, fair or poor control respectively[18]. Where HbA1c values were not available, fasting plasma glucose values were used to determine glycemic control. FPG <126, 126-144, and >144 were taken as good, fair and poor control respectively[18].

Total cholesterol and high density lipoproteins were estimated by CHOD-PAP method while triglycerides was estimated by GPO-PAP method and low density lipoproteins values were calculated [19]. Values of total cholesterol > 200 mg/dl, triglycerides > 150 mg/dl, low density lipoproteins > 130 mg/dl, high density lipoproteins < 40 mg/dl for males and < 50 mg/dl for females were taken as abnormal [20].

Height and weight was recorded by the medical officer with the help of height and weight scale with subjects in light clothing and standing without shoes. Height was recorded to the nearest centimeters and weight to the nearest 0.1 kilogram. Body mass index (BMI) was calculated by the formula, weight in kilograms divided by height in metres square (kg/m^2). Obesity was taken as BMI > 25 kg/m^2 as suggested by the International Obesity Task Force[21].

The OPD medical officer using a mercury sphygmomanometer measured blood pressure once. Hypertension was defined as B.P >130/85 mmHg or isolated systolic & diastolic blood pressure of greater than 130 & 85 mmHg respectively [22].

Patients with history of Ischemic Heart Disease as evident by ECG changes or symptoms deemed sufficient by the physician to be suggestive of angina or MI were termed as sufferers of angina and MI. Those suffering from any macrovascular and Myocardial infarction were labeled in the group of Myocardial infarction.

Patients with history of stroke evident by signs & symptoms and physical examination as assessed by the physician was termed as suffering from stroke. Those if suffering from angina and stroke were labeled in the group of angina.

Peripheral Vascular Disease (PVD) was inferred from absent dorsalis pedis or posterior tibial pulses with/without a history of intermittent claudication. Those if suffering from angina and PVD were labeled in group of angina. Those if suffering from PVD and stroke were labeled in the group of stroke.

Data entry and analysis

Data was entered and analyzed on SPSS 7.5. ANOVA was used for estimating statistical significance of differences in means of continuous variables. Chi-square test was used to assess statistical significance of difference in categorical variables.

RESULTS

Out of total diabetics, 502 subjects (23.3 %) were found to have any of the macrovascular symptoms (MI, 24.9%; angina, 56.7%; stroke, 15.7%; PVD, 2.6%). All available bio-chemical parameters were analyzed and mean values are given in table-1. Only 16.5% of the patients were using any statins. Though the difference was not statistically significant the use was slightly higher among males (17.5%) as compared to females (15.6%) (Table-2). Among older subjects (>60 years of age) 18.6% were using statins whereas in those less than 60 years the use of statins was around 15%. This difference was also statistically non significant. In terms of socioeconomic status use of statins was slightly higher among businessmen and professionals (20% of all businessmen and professionals)) as compared to skilled workers (15.7% of all skilled workers) and housewives (15.6% of all housewives). In relation to vascular disease the use of statins was most frequent among the angina sufferers (20%), followed by those who had MI (16.9%), followed by stroke sufferers (10%) while none of the peripheral vascular disease sufferers were using statins (Table-3).

Table 1: Characteristics of the Sample

	Male	Female
	Mean $\pm$ SD	Mean $\pm$ SD
Age (years)	57.5 $\pm$ 10.2	55.9 $\pm$ 9.7
Weight (Kgs)	70.0 $\pm$ 11.1	63.2 $\pm$ 12.4
Height (metre)	1.70 $\pm$ 0.1	1.50 $\pm$ 0.1

Body Mass Index (Kg/m2)	25.3 ± 3.5	27.1 ± 5.0
Systolic Blood Pressure (mmHg)	131.6 ± 22.4	140.8 ± 24.6
Diastolic Blood Pressure (mmHg)	81.4 ± 11.8	82.1 ± 13.0
Cholesterol (mg/dl)	197.2 ± 47.8	206.5 ± 45.8
Triglycerides (mg/dl)	191.3 ± 131.6	192.9 ± 103.9
Low Density Lipoproteins (mg/dl)	122.6 ± 42.7	131.4 ± 47.4
High Density Lipoproteins (mg/dl)	37.7 ± 9.0	37.9 ± 11.0
Fasting Plasma Glucose (mg/dl)	190.8 ± 80.1	199.6 ± 86.2
Random Plasma Glucose (mg/dl)	256.0 ± 92.4	262.5 ± 105.0
HbA1c (%)	8.7 ± 2.3	9.2 ± 2.3

Table 2: Statin use according to sex of Subjects

	Statin Use	
	Yes	No
Male (n=252)	44(17.5%)	208(82.5%)
Female (n=250)	39(15.6%)	211(84.4%)
Total (n=502)	83(16.5%)	419(83.5%)

Table 3: Statin Use according to Macrovascular disease of patients

	Statin Use	
	Yes	No
Angina (n=285)	55(20.0%)	230(80.0%)
MI (n=125)	20(16.9%)	105(83.1%)
Stroke (n=79)	8(10.0%)	71(90.0%)
PVD (n=13)	0(0.0%)	13(100.0%)

The users of statins had higher values for triglycerides, total cholesterol and LDL-C and lower mean values for HDL-C (figure 1).

DISCUSSION

The results of this study shows a trend which has also been reported by other researchers i.e under prescription of statins [23-24].

Only one fourth of diabetic subjects with macrovascular disease were taking statins for their lipid control. As the duration of treatment for which statins had been prescribed is not known, comments on the effect of use of statins could not be given. The presence of higher proportion of subjects with diabetic dyslipidemia in the statins user group could be either due to the short period since commencement of medication when they presented at BIDE or that they were under-dosed.

Though the differences in the characteristics of the users and non-users did not reach statistical significance the results of this study indicates that males, relatively more affluent, older diabetics, those having angina and having elevated triglycerides are more likely to get treated by statins. Although the subjects presenting at BIDE are from a relatively narrow range of socioeconomic status, housewives seem to be less likely to be started on statin. This trend of females not been started on statins has also been seen in other studies [24-26].

The Health Survey for England and the British Regional Heart Study suggested that most older men with CHD are not receiving lipid lowering drug treatment while in our study the elderly diabetics with CHD were proportionally more on statin treatment; probably as younger subjects were put on diet & exercise and not considered for statins as a first line therapy by the physicians [27].

It is surprising that subjects with angina were more on statins as compared to MI a reverse trend as seen in studies elsewhere. This highlights the fact that subjects with MI were not given statins as a part of therapy irrespective of lipid levels; perhaps having normal lipid levels post MI been a reason for their not been started on statins. Angina patients have a high absolute risk of acute coronary events and silent MI in diabetics advocates for earlier treatment with statins [24-25].

In subjects with type 2 diabetes blood triglycerides tend to be raised and HDL levels reduced even with good metabolic control while LDL levels tend to be similar to those seen in the general population. This has contributed to the belief that LDL is of little relevance to the risk of CHD in diabetics and thus most people with diabetes do not receive lipid lowering drugs despite their increased risk.

The statin user group in our study had markedly higher mean values for triglycerides, total cholesterol & LDL and slightly lower value of HDL. It is suggested that either the subjects were recently prescribed statins or higher doses of the drugs are required in these patients to achieve target lipid levels; both of which could not be verified in this study. By retrieving and analyzing data from a larger and more heterogeneous group of subjects validity of these trends could be verified.

For the current analysis information about previous physicians was not available so any trends in the use of statins by various physicians could not be explored. However despite the clear efficacy of statin use it seems likely that physicians may vary in their knowledge, attitudes and practices regarding the use of statins.

The very low statin prescribing rate in CHD subjects is a cause for concern especially as type 2 diabetic subjects has high morbidity and mortality[11]. Thus there is a need to review the treatment of all diabetic patients with CHD and make sure that patients are receiving the benefits of starting treatment as early as possible.

Barriers to a more wide spread use of statins may include fears about the cost resulting in non-affordability as well as clinical practices. Since 80% of CHD occurs in developing countries it should be a priority to make latest recommendations such as ATP III Report accessible to the physicians[14]. Physicians are aware about the potential gains from the currently available preventive strategies and it is hoped that enough studies have been done to convince physicians that statins should be prescribed for the vast majority (if not all) diabetic patients with CHD in both primary and secondary care.

In conclusion the results of this study verify the low prescribing rates of statins in our community setting. In view of possible detrimental impact of this trend, further studies are needed to identify the factors leading to low use of statins in type 2 diabetic subjects with macrovascular symptoms to ensure that patients receive this treatment which will lead to clinical and public health benefits.

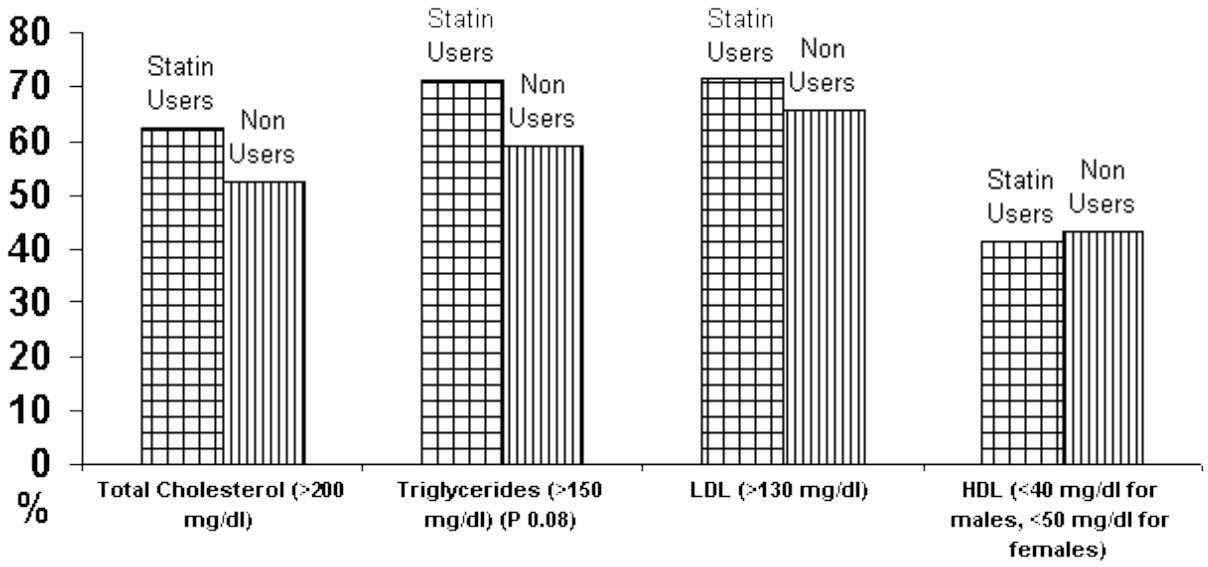

Figure-1: Prevalence of lipid abnormalities according to Statin use

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