FREQUENCY OF HYPERTRIGLYCERIDEMIA IN TYPE 2 DIABETIC PATIENTS RECEIVING STATIN THERAPY AND ITS CORRELATION WITH GLYCEMIC CONTROL

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ABSTRACT

Objective: To determine the frequency of hypertriglyceridemia in type 2 diabetic patients who are on statin therapy and its correlation with glycemic control.

Methodology: This cross sectional study was conducted from December 2019 to July 2020 in the outpatient department of Endocrinology unit, Hayatabad medical complex Peshawar. A total of 99 diabetic patients, who were regularly taking statins for hypertriglyceridemia, were included using non probability consecutive sampling technique. All eligible patients were assessed for hypertriglyceridemia and glycemic status. Data was analyzed with SPSS version 23. Results were presented as tables and bar charts.

Results: Mean age of the patients was 53.2 (SD ± 10.1) years. Males were 54%. The mean duration of diabetes was 5.8 (SD ± 2.1) years, with 59.6% of the patients having duration of diabetes of more than 5 years. The mean body mass index of samples was 26.7 (SD= ± 3.0) kg/m^2. The mean value of glycated haemoglobin (HbA1c) of samples was 8.1% (SD ± 0.05). The frequency of hypertriglyceridemia was 35.4%. HbA1c level had a statistically significant positive correlation with hypertriglyceridemia. Body mass index and duration of diabetes also correlated positively with hypertriglyceridemia, although the correlation was not significant.

Conclusion: A significant percentage of type 2 diabetic patients rceiving statin therapy have hypertriglyceridemia, with glycemic control having a significant impact on triglycerides level.

Key Words: Hypertriglyceridemia, Type 2 diabetes mellitus, Statin therapy, HBA1c

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INTRODUCTION

Diabetes mellitus is a major socioeconomic burden and leading cause of morbidity and mortality. In a survey done by international diabetes federation (IDF) in 2019, around 463 million adults were estimated to have diabetes and they also estimated this number to rise to 700 million by 2045[1]. In Pakistan, an estimated 20 million people are affected by diabetes[2]. Currently Pakistan stands 4th in global prevalence of diabetes and is expected to surpass USA by 2045. Pakistan also has one of the highest mortality from complications of diabetes[3].

Hypertriglyceridemia is a common problem in diabetics, particularly the uncontrolled ones[4]. High triglycerides (TGs) are also commonly accompanied by raised non HDL cholesterol, and this combination of lipid abnormalities is described as atherogenic dyslipidemia of diabetes (ADD)[5]. In Type 2 diabetes both raised blood sugar and insulin resistance leads to raised TG levels. These factors result in increased production and decreased clearance of chylomicrons and VLDL[6]. These TG rich lipoproteins, in addition to LDL, are responsible for formation and progression of atheroma in diabetic patients[6]. So the ADD puts patient at a 3-4 times higher cardiovascular disease risk in comparison to those without diabetes[7].

Hypertriglyceridemia is one of the modifiable cardiovascular disease (CVD) risk factors in T2DM. In order to reduce the CVD risk, TG levels should be less than 150 mg/dl[8]. statins are commonly used in management of

dyslipidemia in diabetics. Almost 32 % of US adults (12 million) who were receiving statins were found to have raised TGs'[9]. A large multi-center audit conducted in UK found that 46.3 % diabetic patients had high TGs', despite taking statin therapy[10]. In another study the frequency of hypertriglyceridemia was found to be 36% in type 2 diabetic patients on statin therapy[11].

American heart association task force on clinical guidelines indicate that all patients with diabetes 40 to 75 years of age with an low density lipoprotein (LDL)-C more than 70 mg/dl should be treated with a statin[12]. Although statins effectively reduce the LDL and total cholesterol levels, they may not be as effective in controlling serum triglyceride levels. Also total triglycerides may be a more powerful predictor of coronary heart disease than total cholesterol in type 2 diabetic subjects[13]. Thus, it is possible that hypertriglyceridemia is a better marker of risk in this group of subjects[14]. For this reason it is also important to address hypertriglyceridemia on equal footing with LDL-C to address this residual CVD risk in Type 2 diabetics.

The purpose of this study was to assess the burden of hypertriglyceridemia in Type 2 diabetes despite them being on statins. This particular subject (where patients are already on statins) has not been explored in local settings. This shall help us in devising a cumulative approach towards managing this independent CVD risk factor in local type 2 diabetic population

METHODOLOGY

This descriptive cross-sectional study was conducted in the outpatient department of Diabetes and Endocrinology, Hayatabad Medical Complex, Peshawar from December 2019 to July 2020. Sample size was estimated using online sample size calculator for proportion , available at www.openepi.com, version 3.01, taking 36% prevalence of hypertriglyceridemia, 10% margin of error and 95% confidence interval, thus requiring at least n = 89 samples for this study. However we took 99 patients[11]. It was approved by the institutional research and ethical committee. A written informed consent was obtained from all patients. Using non probability consecutive sampling technique, Patients aged 30 - 75 years, either gender, with type 2 diabetes, on statin therapy for at least 03 months were included. All the relevant information including demographics details, body mass index (BMI), duration of diabetes, triglycerides levels, and HbA1c were obtained on a pre-designed pro-forma. Dose requirement was 10-20 mg atorvastatin or equivalent. Patients with any concomitant disorder or confounder (factors that can significantly alter triglycerides levels) like significant renal impairment (eGFR <30ml/1.73m^2), associated uncontrolled hypothyroidism, drugs use such as estrogens and alcohol addiction were excluded. Also patients with HbA1c more than 9.0, incomplete medical record, poor compliance and smoking were excluded. All biochemistry work up (including HBA1C, lipid profile, urea, creatinine, electrolytes and thyroid stimulating hormone levels) were conducted using Roche Cobas C501 chemistry analyzer. Hypertriglyceridemia was defined as serum TGs' level of more than 150 mg/dl.

Data was stored and analyzed using IBM SPSS version 23.0. Counts with percentages were given for qualitative data sets, mean with standard deviation were determined for all quantitative parameters. Pearson correlation analysis was used to check correlation of hypertriglyceridemia with duration of diabetes, body mass index (BMI) levels and HbA1c. Independents sample t-test was used to compare the mean between hypertriglyceridemia and non-hypertriglyceridemia samples. P-values less than 0.05 was considered statistically significant. Results were presented in the form of tables and charts.

RESULTS

There were 99 patients having mean age of 53.2 (SD ±10.1) years, including 54 male and 45 females. The mean duration of diabetes was 5.8 (SD ± 2.1) years, with 59.6% of the patients having duration of diabetes of more than 5-years. The mean BMI of samples was 26.7 (SD= ± 3.0) kg/m^2, among them 63.6% had BMI of more than 23 kg/m^2. The mean value of HbA1c of samples was 8.1% (SD ± 0.05), among them 55.6% had an HbA1c range of 8.1 – 9.0 %. The mean level of serum triglyceride levels was 150.6 mg/dl (SD ± 49.8). The Frequency of hypertriglyceridemia was 35.4 %. Table 1 shows hypertriglyceridemia and normal triglycerides samples with respect to studied parameters. Triglyceride levels gave 15% positive correlation with age, 19.3% positive correlation with BMI and 28.4% positive correlation with HbA1c as shown in Table 2. The mean values for age, BMI, duration of diabetes, HbA1c and TGs' were found higher among patients with Hypertriglyceridemia as compared to patients with normal triglycerides (Table 3).

DISCUSSION

Our study found that hypertriglyceridemia is common among people with T2DM visiting tertiary care center despite taking statin therapy. The results of our study are consistent with some studies conducted internationally[9,11]. In other studies the prevalence of hypertriglyceridemia in diabetics patients receiving statins was much higher as compared to our study[10,15,17]. We also found a significant correlation between hypertriglyceridemia and HBA1c. Similar results were reported in a study conducted at a tertiary care centre of Karachi but those patients were not on statins therapy[16].

In the present study, Rosuvastatin was the most frequently prescribed statin, the other being Atorvastatin

Table 1: Hypertriglyceridemia with respect to studied parameters

Parameters		Hypertriglyceridemia			
		Yes (n=35)		No (n=64)	
		n	%	n	%
Duration of Diabetes	≤ 5 years	11	31.4	29	45.3
	>5 years	24	68.6	35	54.7
BMI	< 23 kg/m2	12	34.3	24	37.5
	≥ 23 kg/m2	23	65.7	40	62.5
HbA1c	≤ 7 %	1	2.9	2	3.1
	7.1 - 8.0 %	12	34.3	29	45.3
	8.1 - 9.0 %	22	62.9	33	51.6

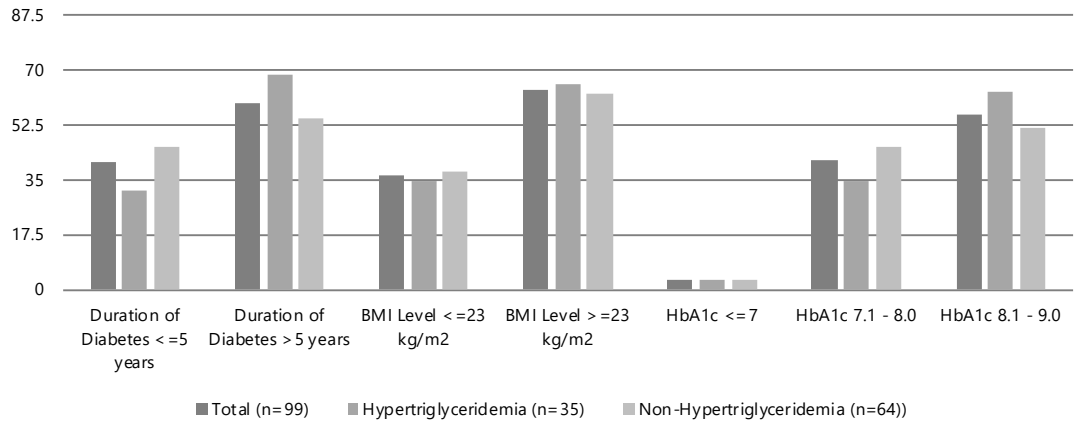
Table 2: Correlation analysis of studied variables

Parameters		Triglycerides	p-value
Age	Pearson Correlation	0.015	0.88
BMI	Pearson Correlation	0.193	0.19
HbA1c	Pearson Correlation	0.284	0.004*
*p<0.05 was considered statistically significant for correlation			

Table 3: Mean comparison of studied parameters

Parameters	Hypertriglyceridemia (n=35)		Non-Hypertriglyceridemia (n=64)		p-value
	Mean	SD	Mean	SD	
Age (years)	53.9	11.6	52.9	9.2	0.64
BMI (Kg/m2)	27.0	3.0	26.6	3.0	0.52
Duration of Diabetes (Years)	6.2	2.2	5.7	2.1	0.27
HBA1C (%)	8.3	0.6	8.1	0.6	0.08
Triglycerides (mg/dl)	206.3	38.2	120.2	20.4	<0.01*
*p<0.05 was considered statistically significant using Independent sample t-test					

Figure 1: Baseline characteristics of studied parameters (n=99)



and in some patients, simvastatin. In our study, the minimum / moderate intensity statin therapy was used (10-20 mg atoravastatin or equivalent)[17]. Similar differences in statin prescription were observed in another study, i.e. Dyslipidemia International Study (DYSIS-Middle east) in which simvastatin 20-40 mg/dl or equivalent was most commonly prescribed regimen and the frequency of hypertriglyceridemia was reported to be 48.5%[18].

We used a cut off of 150 mg/dl for triglycerides while there are studies investigating the CVD risk at lower levels. This was noted in a study conducted in Denmark, where patients with TGs' levels between 89-176 mg/dl had a significantly increased risk of CVD as compared to those with levels less than 89 mg/dl[19].

The cardiovascular benefits of triglycerides control and need for further lipid lowering therapies was also addressed in the famous Reduce-It trial, where the use of marine omega 3 (Icosapent ethyl (IPE)) resulted in lower triglyceride levels and significant CVD risk reduction in patients who were already receiving statin therapy. These benefits were consistent in diabetics as well[20].

No other lipid lowering agents have been shown to reduce cardiovascular risk when given in addition to statins. Two large cardiovascular outcome trials in hypertriglyceridemic patients (AIM-HIGH and HPS2-THRIVE) studied the use of extended release Niacin added to statins and both failed to show any significant CVD benefit[21,22]. Pemafibrate is a new fibrate under investigation in diabetics patients and may show benefits for TGs and possibly CVD risk reduction[23].

Lifestyle measures are equally important in patients with type 2 diabetes in order to achieve glycemic control, as well as reduce TG levels. Studies have found that there is a significant (25 %) TG reduction in patients who are able to lose 5-10 % of body weight with expected beneficial effects on glycemic control as well[24,25].

Higher intake of unsaturated fat and proteins along with low carbohydrates results in lower triglyceride levels[26]. In general, carbohydrates in all forms are well known to cause raised TG levels. This was demonstrated in a recently concluded randomized controlled trial, where a reduction in carbohydrate intake lead to low TG level and reversal of metabolic syndrome[27-29]. Similarly both aerobic and resistance exercises have shown benefits in lowering TG levels individually as well as enhanced efficacy in combination[30,31].

CONCLUSION

A large proportion of diabetic patients have hypertriglyceridemia and they remain at high CVD risk regardless of statin use. A comprehensive approach including good glycemic control, lifestyle modification and medication adherence, in addition to statin therapy is required. Additionally, the benefits of novel evidence based treatments for hypertriglyceridemia like Icosapent ethyl, need to be explored in local population.

LIMITATIONS

Our study has certain limitations. The cross sectional nature of this study prevents any assessment of the dose response relationship between statins and triglyceride levels. Although glycemic control had a significant impact on triglyceride levels, it is difficult to obtain a definitive conclusion about associations and correlations in a small cross sectional study. Conducting such a study on a large multi-center level shall further help overcome these limitations and consolidate our knowledge about this topic in local settings.

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CONTRIBUTORS

ZU conceived the idea, wrote initial manuscript, collected data and finalized the draft. SEM and TG helped correction of the proposal, literature search, data collection, interpretation and overall supervision of the project. SK, AN and AA provided technical support, helped in data interpretation and provided expert guidance where needed. All authors contributed significantly to the submitted manuscript.