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ORIGINAL ARTICLE

A Cross Sectional Study of Glycemic Status in Diabetics Taking Statins

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ABSTRACT

In this case research, an effort was made to analyze the diabetogenic statins effect, as well as the way this is associated with different comorbidities associated.

Study Design: Cross-Sectional Study
Place of Study: Punjab Institute of Cardiology Lahore.
Duration of Study: October 2020 to March 2022
Materials and Methods: This cross-sectional study was conducted at the Department of Cardiology between October 2020 to March 2022 for duration of one year and Five months in order to collect the necessary data. Participants were required to have had normal blood sugar levels when they began taking statins and to have been on statins for at least one year prior to eligibility. Those who had never been diagnosed with diabetes mellitus were more likely to get the condition as a result of this study, according to the findings new Onset Diabetes Mellitus (NODM). Both the glucose and insulin concentrations in the blood were subjected to estimation. The subjects saw and reported additional adverse effects caused by statins and comorbidities associated with them. To meet the objective of analyzing adverse reactions to drugs, descriptive statistics were required.
Result: The most commonly prescribed dosage for statins was 40mg of atorvastatin, according to the statistics. Diabetes was detected in roughly 25 percent of patients on 80mg of atorvastatin.
Conclusion: The use of statins is related with a risk of non-alcoholic fatty liver disease ranging from low to significant (NODM). The amount of statin medication a person takes is one of the most influential contributors to the increase in diabetes risk linked with statin use.
Keywords: Hyperglycemia, newly diagnosed diabetes, statins, and type 2 diabetes

INTRODUCTION

The distribution of disease burden has abruptly shifted away from communicable diseases and towards no communicable diseases since the turn of the century. The World Health Organization (WHO) forecasted in its Global Action Plan 2013 that by the year 2020, noncommunicable diseases will present eighty percent of the total global disease burden. In impoverished nations, these diseases will be responsible for seven out of ten deaths, with fifty percent of these deaths occurring in those less than seventy years of age. [1] In Pakistan, from 1990 to 2020, the number of premature deaths attributable to heart diseases (CVDs) increased from 23.2 million to over 37 million; this is a significant increase in the number of premature deaths attributable to CVDs. 1948's Framingham Heart research showed an association between the development of cardiovascular disease and hypercholesterolemia. As a direct result of the previous investigation, scientists concluded that the enzyme known as 3-hydroxy-3-methylglutaryl-CoA reductase is rate-limiting enzyme as well as natural target found in the cholesterol synthesis process.

As a result, statins have become the most popular and effective treatment option for CAD patients. The investigation was conducted between 2006 and 2010. This was deemed significant in view of the growing threat posed by CAD on a continental and global scale (CHD). Current research indicates that a high TC/HDL ratio and low HDL-C is one of the most important risk factors for coronary artery disease (CAD), and Pakistanis share the same lipid profile pattern as other individuals with this combination. It has been depicted that Pakistanis have the least levels of high-density lipoprotein cholesterol (HDL-C). [5] As a result, it is recommended that people residing in South Asia take statins regularly and consistently. The recent link between statins and the onset of new-onset diabetes, often known as NOD, has attracted the experts' interest considerably. Many studies have demonstrated that disruptions in insulin signaling pathways, decreased insulin secretion, and/or a decrease in the body's general insulin sensitivity increase the risk of neurodegenerative disease. All three of these conditions can raise the probability of having NODM. In light of this earlier research, the goal of the current study was to examine the glycemic status of individuals who were already taking statins.

MATERIALS AND METHODS

A prospective observational study was conducted over the course of one and a half years in the Cardiology Department. (October 2021–March 2022). Prior to initiating the research project, the approval from Ethics Committee's was first sought. After that, consent was taken from every subject prior to their joining.

Participants were deemed eligible for the study if they met the following criteria: they had to be at least 30 years old, they could be of either gender, they had to have been on statins a year at least, and their blood glucose fasting level had to be less than 100 mg/dl when the statin was initially prescribed. Individuals who were already taking drugs that had the potential to increase their glucose blood levels, such as beta-blockers, fluoroquinolones, glucocorticoids ,atypical antipsychotics, protease inhibitors and thiazide diuretics were excluded from the trial. This included type 1 diabetic individuals. In addition, diabetics, pregnant women, and mothers with young children who were still breastfeeding were not authorized to participate. It was vital to gather a complete medical history, and while doing so, special attention was paid to the patient's family history and any relevant risk factors connected with metabolic syndrome. We collected the patient's demographic information, clinical characteristics, and drug history by following the instructions on this pro forma.

The basic outcomes of the reseach were the progression to non-obese diabetic mellitus (NODM), also known as diabetes in people who are not overweight, and the development of pre diabetes. Throughout the experiment, the blood glucose levels of the individuals were measured, recorded, and analyzed. Blood samples were taken from each and every patient who had developed diabetes while fasting in order to determine the levels of glucose and insulin present in their bodies. The homeostatic model assessment (HOMA) is a computerized model that can be used as a tool to predict insulin sensitivity and β cell activity this model is derived by applying the following equation, was used to shed light

on a potential cause for the onset of diabetes. The following equation was utilized to get this conclusion: [8]

$$\text{HOMA insulin resistance} = \frac{\text{Fasting glucose X Fasting Insulin}}{22.5}$$

By applying the following formula to the calculation, we were able to determine the quantitative insulin sensitivity check index (QUICKI):

$$1/[\log(\text{fasting insulin } \mu U/ml) + \log(\text{fasting glucose mg/dL})]$$

Microsoft Corporation's Excel 2016 and IBM Corporation's SPSS version 23 were used to analyze the data. This type of license is referred to as trialware. For the purposes of establishing a baseline and gathering demographic information, a descriptive analysis was conducted. When data exhibit a regular pattern, the value of continuous variables can be stated as the variable's mean combined with its standard deviation. Numbers of patients and corresponding percentages (n,%) were used to represent categorical factors that were determined to be of a categorical nature. Notwithstanding the skewed nature of the data, it was decided to publish them using a median and interquartile range (quartile 1 and quartile 3). The study's conclusions included a breakdown of risk factors by frequency as well as by percentage. Using descriptive statistics allowed for a study of adverse drug effects (ADRs). Due to the small sample size, the Cox regression model and survival analysis for calculating the hazards ratio was unable to be performed in this research. These two models are utilized to calculate the odds ratio. Due to this, it was unable to reach conclusive conclusions regarding these topics. As a direct consequence of this, descriptive statistics become an inescapable requirement.

RESULTS

A total of 102 patients were invited to participate in the investigation in accordance with the rules that had been established beforehand. A pre structured pro forma was utilized to collect both the patient's demographic information and clinical information. The demographic parameters that were considered at the outset of the research project are presented in [Table 1] as the patients number (n) and the corresponding percentage. As seen in [Table 1], patients are required to take a variety of different drugs simultaneously. Males constituted 63.5% of the study population, while there were 37 females out of a total of 65 male participants. At least 60-year-olds but not yet 65-year-olds constituted the vast majority of the population.

Statins were supplied to a total of 102 individuals, and the results revealed that 8 of these patients acquired diabetes mellitus (DM) and 4 of these individuals had pre diabetes. These figures represent increases of 7.7% and 3.8%, respectively.

In the present study, participants utilized a variety of statins at a variety of dosages, which are all illustrated in [Figure 1]. Atorvastatin most commonly prescribed dosage of 40 mg , whilst atorvastatin in dosages of 80 mg was the least frequently prescribed statin. Eight patients who were taking 80 mg of atorvastatin at the time of the investigations had a 25% increased risk of developing diabetes, according to the results of additional research. While not any of the patients who took rosuvastatin 20 mg acquired prediabetes or diabetes, 4.1% of those who took atorvastatin 20 mg and 14.7% of those who took atorvastatin 40 mg developed non-alcoholic fatty liver disease (NODM). 59 patients, or 56.7% of the total, had a body mass index (BMI) within the normal parameters; 29 patients, or 27.9% of the total, had a BMI within the overweight range; and 8 patients, or 7.7% of the total, had a BMI within the obese range while being underweight.

The only form of lipid profile collected was a single point profile, and the frequency distribution with respect to lipid profiles among individuals can be depicted in [Table 2].

52.6% of the population smoked cigarettes, 63.2% had a first-degree diabetic relative, and 47.4% had a family history of cardiovascular disease. In addition to suffering from a variety of other mental disorders, 15.4% of patients were also diagnosed with mild depression. It was shown that 68.4% of patients did not engage in any sort of physical activity, whereas 31.6% of patients participated in low-to-medium intensity exercise. The individuals with several diseases depict 21.1% insulin resistance. Among these diseases were: This group included polycystic ovarian disease and acanthosis nigricans as two of its diseases. Our study group's average waist circumference was 86.41 cm, with a standardized deviation of 9.13 cm.

An analysis of the spectrum of adverse effects experienced by the study's subjects: There was a total of 33 patients who developed ADRs out of a total population of 102, which represents 31,73% of the total. Myalgia was the adverse drug reaction that occurred in the population with the highest frequency, and it was caused by statin therapy (46.88%). [Table 3] presents an overview of the plethora of adverse effects identified during the experiment among the participants. The WHO-UMC causality evaluation scale was utilized to characterize adverse drug reactions (ADRs) linked with statins, and the results are presented in [Table 3]. ADR is abbreviation for adverse drug response.

A review of the impact of statin therapy on insulin resistance, including an assessment of the homeostatic model and the quantitative insulin sensitivity check index: If the HOMA value is greater than 2.27, it suggests that the patient has insulin resistance. Ten individuals developed diabetes, and 83.3% of them had HOMA scores greater than 2.27. This indicates that insulin resistance may be a risk factor for the development of diabetes in statin users. If a patient's QUICKI score was greater than or equivalent to 0.357, then substantial insulin resistance was found. There were eleven individuals with substantial insulin resistance.

Table 1
Baseline demographic parameters of patients included in the study

Patient characteristics	Number of patients	Percentage
Male/Female	63.73/36.27	63.73/36.27
Mean age (years)	61.19±10.04	
Hypertension	99	97.06
Hypercholesterolemia	100	98.04
Overweight/obese	36	35.29
Ischemic heart disease	69	67.65
Concomitant medications		
Antiplatelet drugs: Aspirin	91	89.22
Clopidogrel	31	30.39
Diuretics (except thiazide diuretics)	16	15.69
Antianginal drugs	12	11.76
ACEIs/ARBs	93	91.18
Others	8	7.84

Values are expressed as number of patients and percentage. ARBs=Angiotensin receptor blockers, ACEIs=Angiotensin-converting enzyme inhibitors

Table 2
Mean distribution of lipid profile in the study population

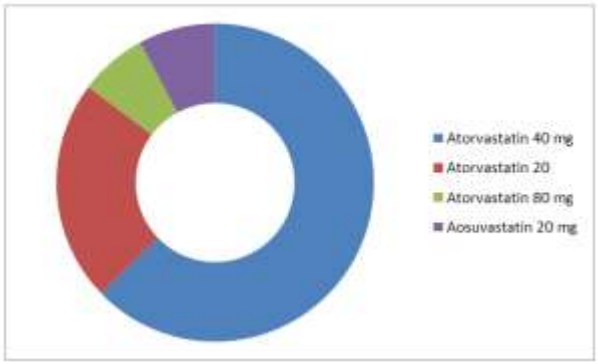
Parameters	Mean±SD
Triglycerides (mg/dl)	136±39.92
HDL (mg/dl)	36.98±6.75
LDL (mg/dl)	129.69±41.89

Table 3 Side-effect profile of patients on statins

ADRs	Number of adverse reactions	Out of total 32 adverse effects (%)	Causality assessment
Myalgia	15	46.88	Possible
Tingling sensation	7	21.88	Possible
Headache	5	15.625	Possible
Loss of appetite	2	6.25	Possible
Dizziness	2	6.25	Possible
Hepatitis	1	3.13	Probable

Values are expressed as number of adverse reactions and percentage. ADRs=Adverse drug reactions

Fig No 1 Percentage use of different types of statins in the study population



DISCUSSION

In a number of regions around the globe, including Pakistan, cardiovascular diseases are among the leading causes of mortality. Statins, which are now the most effective medications for treating hypercholesterolemia, play a crucial role in both the primary and secondary prevention of cardiovascular illnesses. In recent years, there has been increased consideration regarding the link between statin use and the onset of diabetes. This difficulty arises as a result of the association between the two. [11] Because statins are prescribed commonly type of medication and diabetes influence a significant portion of the world's population, it is crucial that the nature of the link between the use of statins and an increased risk of developing diabetes be brought to light so that it can be fully comprehended. Under the boundaries of this conceptual framework, the current study was conducted to determine whether or not statins affect the glycemic status of non-diabetic individuals who had been taking statins for at least a year. In addition, the purpose of this study is to assess the relationship between statin use and diminished insulin sensitivity. [12]

According to the results of a study conducted by Sattar and colleagues, non-diabetic individuals who use statins have a nine percent greater chance of developing diabetes in the future. [14] Several demographic indicators, including ageing, weight gain, and the development of metabolic syndrome, can reliably analyze the onset of diabetes mellitus. These characteristics are linked with a twelvefold increase in the risk of type 2 diabetes and a threefold increase in the risk of atherosclerosis. Diabetes mellitus is a form of diabetes characterized by an accumulation of sugar in the blood. Hence, the statins usage can identify diabetes in individuals owing additional risks. [15]

This analysis focused on a population with a mean age of 62.26 years and a standard deviation of 10.02 years. The Anglo-Scandinavian Cardiac Outcomes Trial – Lipid-Lowering Arm (ASCOT-LLA) and the study conducted by Aiman et al.[16] yielded comparable results. In the first research, patients were on average 63 years old when they were diagnosed with diabetes, whereas in the second study, patients were on average 66 years old. In addition, studies conducted by Sattar and his colleagues revealed that those between the ages of 55 and 76 were more susceptible to developing diabetes. [14] Both Preiss et al. and Navarese et al. reached the same conclusion, namely that those aged 55 to 65 had an elevated chance of having diabetes. [17],[18] In the scope of this study, 63.5% of male patients were found to be using statins, which is a significantly greater proportion than that of female patients. At the conclusion of the ASCOT-LLA experiment, the researchers determined that around 81% of those who participated were male. [19],[20],[21] In the current study, 56.7% of patients were found to have a normal body mass index (BMI), 27.9% of patients were found to be overweight, and 7.7% of patients were found to be either obese or underweight. This result is consistent with the findings of Cassuto and colleagues, who discovered that both statin therapy and obesity are associated independently with an increased diabetes development risk , and who discovered that both of these factors independently increase the risk for developing diabetes. [22] Despite this, a much larger proportion of overweight individuals participated in the clinical research conducted by WOSCOPS, LIPID, HPS, and ASCOTT. It has been demonstrated that this is the most plausible explanation for why the proportion of individuals with diabetes was higher in earlier trials than in the present study. According to the findings of a study conducted by Laakso and Kuusisto, the BMI of those who took statins increased by 1,3 whereas the BMI of individuals who did not take statins increased by just 0. (P 0.02). Recent research indicates that those who used statins suffered a more rapid increase in their body mass index (BMI) and consumed more calories and fat than those who did not take statins. [23] Although the creation of NODM was anticipated to be the principal outcome of our analysis, we spent the majority of our time concentrating on its development. 7.7% of patients (out of a total of 8) acquired nonalcoholic fatty liver disease and 3.8% of patients (out of a total of 4) developed pre diabetes during the course of four years. The statin most frequently associated with non-alcoholic fatty liver disease (NODM) was atorvastatin 80 mg, a higher-potency form of the drug. In the PROSPER study, which compared pravastatin 40 mg to a placebo over a median of 3.2 years, the group that took the statin had a 6.6% incidence of non-alcoholic fatty liver disease (NODM). It was shown that the amount of statin taken affected the diabetogenic potential of the medicine.

After a median follow-up time of 4.9 years, Preiss et al. revealed in a 2011 meta-analysis that greater potency statins are associated with a 13% increased risk of non-alcoholic fatty liver disease (NODM) compared to lower potency statins. The researchers reached this conclusion after comparing the two forms of statins (odds ratio 1.12, 1.04–1.22).[17]

Individuals with a high number of the key risk factors have an increased likelihood of acquiring NODM. The diabetes onset with atorvastatin 80 mg, rosuvastatin 20 mg, and pravastatin 40 mg was around 15%, 25%, and 7%, respectively, according to a meta-analysis conducted by Navarese et al. This data was extracted from the studies included in the investigation. [18] According to the findings of five population-based studies, the prevalence of this illness may range from 18% to 99%. [24],[25].Of the several statins that were available, atorvastatin 40 mg was the one most frequently prescribed to our patients. This was due to the fact that it posed the lowest risk of side effects. Approximately 62.75% of patients (n = 64) were taking atorvastatin 40 mg, 22.55% of patients (n = 23) were using atorvastatin 20 mg, 6.86% of patients (n = 7) were taking atorvastatin 80 mg, and 7.84% of patients (n = 8) were receiving rosuvastatin 20 mg. This is consistent with a research done by Koh et al., who hypothesized that atorvastatin 80 mg was linked with a higher onset of diabetes mellitus in the population study and that a dose-dependent impact had been observed. This finding confirms the findings of the study conducted by Koh et al. The findings previously described offered proof for this claim. [26] The ASCOT-LLA, LIPID, and PROSPER trials all reached the same conclusion: higher dosages of statins, such as atorvastatin 80 mg, are associated with a greater risk of acquiring diabetes than lower dosages, such as atorvastatin 10 mg, 20 mg, and rosuvastatin 5 mg, which are less potent overall. This finding was achieved despite the fact that smaller doses of statins carry a decreased risk of adverse effects [27],[28]. In this trial, only atorvastatin and rosuvastatin, two types of statins, were used to reduce patients' cholesterol levels to a healthy range. In various parts of Pakistan, atorvastatin is the mostly utilized statin, which is followed by rosuvastatin and simvastatin, according to data on medicine use. Research examining the use of statins, with the exception of these two, are quite rare.

Male Participants in the Metabolic Syndrome research who had atorvastatin doses ranging from 40 to 80 mg and simvastatin doses ranging from 10 to 20 mg had a 46% more risk of acquiring diabetes mellitus during the duration of the study's median follow-up time of 5.9 years. This was discovered by comparing the

diabetes risk of the patients before and after receiving the drugs. In order to obtain an appropriate measurement of insulin sensitivity, the study was done on a total of 8749 healthy male participants. A decrease in insulin sensitivity of approximately 24% and a decrease in insulin secretion of approximately 12% (P 0.01) were seen in the group of diabetics treated with statins. [29] According to the findings of a study conducted in Korea, those who took statins for a median of three years had a significantly higher chance of developing non-alcoholic fatty liver disease (NODM). [30]

Individuals in our study group were more likely than the general population to suffer from comorbidities such as hypertension and hyperlipidemia. 97.06% & 98.04% of patients were found to have both of these illnesses respectively. This was same with the results of the Collaborative Atorvastatin Diabetes Study, or CARDS research. In that research, the hypertension was seen 84% higher in the atorvastatin group as comparison to placebo group [31]. This was consistent with the results of the CARDS trial. According to the Framingham Heart Study, those with a family history of cardiovascular disease had a considerably increased chance of developing , hyperglycemia ,obesity, dyslipidemia and high blood pressure. This was one of the study's primary conclusions. Relationships between individual behaviour, genetic features, and environmental circumstances might could serve as a possible cause of cardiovascular disease. [32]

Insulin resistance is characterized by a diminished physiologic response to insulin, and this trait is present regardless of whether insulin levels are normal or increased. Many medical disorders, including polycystic ovary syndrome, atherosclerosis, fatty liver disease, obesity, acanthosis nigricans and skin tags have been linked to it. It was found that 21.1% of patients suffered from a range of insulin resistance-related illnesses. Evaluation of the patient's waist circumference, often known as WC, has been shown to be a valid predictor of clinical outcome in a number of extensive epidemiologic studies. The American Diabetes Association has made it clear that waist circumference measurement adds to the predictive value of BMI for diabetes, coronary heart disease, and mortality rate. This added value results from the measurement's capacity to differentiate between persons with comparable BMI. This added value is in addition to and exceeds what BMI provides. [33] The examined population had an average waist circumference of 86.41 cm and a standard deviation of 9.13 cm.

There were a total of 33 adverse reactions recorded across the entire study population. The most frequently reported symptom was myalgia (46.88%), followed by tingling (21.88%). The sole adverse drug reaction (ADR) that required the patient to cease use of the medicine was statin-induced hepatitis. During this evaluation, both myopathy and rhabdomyolysis were eliminated as potential reasons of the patient's complaints. The Naranjo ADR Probability Scale was utilised in order to determine the potential causes of adverse events. [34] Using these scales, it was determined if the bad effects were certainly related with the drug, whether they were probably associated with the medication, whether they were perhaps associated with the medication, and whether they were questionable. It was believed that the usage of statins contributed to each of the adverse reactions that were documented. According to the Hartwig Severity Assessment Scale, the severity of each adverse event ranged between levels 1 and 2, indicating that they were all rather mild. [35] Even though there was only one case of statin-induced hepatitis for which a convincing causal relationship could be established, the medicine was removed from the market out of an abundance of caution.

Insulin resistance is defined as a HOMA score of 2.27 or above, and 83.3% of the candidates in the research who developed diabetes mellitus owned a HOMA score of 2.27 or higher. A HOMA score greater than or equal to 2.27 indicates insulin resistance. The current study defines severe insulin resistance as a QUICKI score of 0.357 or less, and the researchers determined that 83.3% of patients suffered from severe insulin resistance. This could be interpreted to suggest that insulin resistance is the underlying mechanism at play in diabetes caused by statins. This suggested mechanism may be one of the numerous ways in which statins enhance the probability of developing diabetes.

The fact that only a few of research in Pakistan have studied the link between statins and NODM in individuals from that country is one of the study's primary arguments. Current study has demonstrated a link between statins and the illness known as nonalcoholic fatty liver disease in the Pakistani population (NODM). In an effort to shed light on these aspects, this study also included an analysis of the several factors that lead to hyperglycemia in this patient population. In addition, numerous risk factors for nonalcoholic fatty liver disease (NODM) in statin-treated patients have been investigated.

The most significant restriction of this research analysis was the tiny size of sample that we employed. The size of sample was determined by using an incidence rate of 6%, which was approximated based on the findings of prior studies. This rate was utilized as the determining factor. Unfortunately, a survival analysis was not possible to be conducted since the size of sample was insufficient to determine whether or not there was a statistical relationship between the risk factors. This prevented the study from being finished. Because this is a cross-sectional study, it can only demonstrate a correlation between statins and NODM, rather than a causal relationship as would be the case with a longitudinal analysis. Measurements were taken of both the exposure and the result at the same instant.

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