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The Risk of Developing New Onset Diabetes Mellitus (Diabetogenicity) in Statin Treated Patients

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Abstract
Despite the fact that statins are currently the preferred medical treatment for the primary and secondary prevention of cardiovascular disease as well as the treatment of hyperlipidemia, many recent research evidences suggested that statin therapy can have adverse effects on patients' glycemic control as well as increased risk of NOD. The results of these studies, though, are somewhat inconsistent. This study aims to look into how statin exposure affects FBG levels and HbA1c levels, Furthermore, we want to draw attention to the elements that influence statins' ability to cause diabetes.
This retrospective cohort study was carried out at the Benghazi National Heart Center (NHC) from March 2021 to December 2021. 200 patients [143 men (71.5%), 57 women (28.5%)] They were divided into 2 groups. The first group includes CHD patients on Atorvastatin for more than 2 months. The second group includes CHD patients not taking any statin medication. Any known diabetic case was excluded from both groups. FBG and HbA1c were measured for both groups. In addition, the correlation between statin exposure and FBG-HbA1c was measured along total cholesterol (TC), triglycerides (TG), ALT and AST.
Out of 100 participant taking atorvastatin we find 36 (36%) cases of NOD compared to 7 (7%) cases with NOD in the Non-statin group. Patients were sub-divide into groups according to dose of atorvastatin .it was 18 NOD case out of 77 (23.4%) for 40 mg/day and 7 NOD case out of 23 (30.4%) for 80 mg subgroup.
Statin therapy is at least partially to blame for the emergence of newly diagnosed type 2 diabetes mellitus. In this study, Atorvastatin has a dose-dependent diabetogenic effect, which tends to increase the FBG and HbA1c. However, other variables such as age, obesity and the presence of any element of metabolic syndrome augment or amplify this effect. It is necessary for patients on statin therapy, especially those with multiple risk factors such as obesity, metabolic syndrome, and pre-diabetes, should have their glycemic status checked regularly for early detection of any unfavorable alterations in blood glucose levels.
Key words*: Statins, New-Onset Diabetes, Atorvastatin, Hyperlipidemia.*

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I. Introduction

Diabetes is one of the major health problems worldwide. The prevalence of diabetes has substantially increased all around the globe, with recent estimates in adults were about over 537 million individuals (Asamoah et al., 2019). Diabetes not only affects human health but also poses a financial burden, for instance treatment Type 2 diabetes (T2D) common complications (nephropathy, neuropathy and retinopathy) may cost eight hundred billion US dollars/year (International Diabetes Federation, 2009 and Seuring et al, 2015). There is a shortage of data in regard to diabetes data in Libya. Early evidence raised the alarm about diabetes and concluded that it became a serious public health issue in the country. In Benghazi-Libya, a random screening of 868 individuals revealed that about 8.5 % over the age of 20 years were glucose intolerant, about 14% had diabetes. (Kadiki and Roaed, 2001). Diabetes is a metabolic disorder in which, carbohydrate, protein and lipid metabolism substantially disturbed. Obesity is a contributing factor for insulin resistance and diabetes as well as cardiovascular disease.

Cholesterol is essential for human body; it composes 30% of the cell membranes where it controls the fluidity. Normally, a man weighing 68 kg is capable to synthesizes about synthesizes about 1,000 mg (one gram) of cholesterol per day, and the total body content of cholesterol is about 35 g. Whereas the dietary cholesterol intake is about 307 mg/day in the United States (National Health and Nutrition Examination Survey). Increased serum cholesterol levels cause atherosclerosis and considered as a main contributing risk

factor for cardiovascular diseases (CVD). Mainly the cholesterol content of the increased low density lipoprotein (LDL) contributes to CVD more than that of the high density lipoprotein (HDL) (Brunzell et al. 2008).

Statins are the well-known drugs for treatment of hypercholesterolemia and they also reduce the higher levels of serum triglyceride (hypertriglyceridemia). They exert their action via inhibiting the rate-limiting step of cholesterol biosynthesis which is catalyzed by 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (Grundy 1988, Maron et al. 2000). Statins have been found to prevent CVD events (the first and the recurrent events) in patients including diabetics (Catapano et al. 2016). Statins are considered as a safe drug and well tolerated by patients (Armitage 2007). However, statins have been implicated with higher risk of insulin resistance (IR) and elevated incidence of new-onset diabetes type 2 (NOD2). The correlation between statins and increased risk of NOD2 incidence was shown in large cohort studies (Carter et al. 2013, Casula et al. 2017). Nowadays there are 7 common classes of statins used in clinical practice. Among these, Atorvastatin (Lipitor) is regarded as the most popular statin (Vagelos,1991).

The association between using rosuvastatin 20 mg/day and the incidence of new-onset diabetes (25% higher risk of NOD) in patients with metabolic syndrome was firstly documented by Ridker et al. (2008) in the prospective primary prevention trial. This early trial follow by many studies, clinical trials and meta-analysis that showed similar findings and suggested that the long duration of the treatment with statin lead to more NOD cases than short duration (Culver et al. 2012, Crandall et al. 2017, Sattar et al. 2010). According to our knowledge, the diabetogenic effect of statins on Libyan patients who are suffering from hypercholesterolemia is not investigated yet. The aim of the current study is to test the diabetogenicity of statins among hyperlipidemic patients with ischemic heart disease attending National Heart Center of Benghazi in the second largest city in the east of Libya.

II. Material and Methods:

Subjects:

A total of 200 Libyan women and men were included in this study. This study was carried out in Benghazi National Heart Center (NHC), from March 2021 to December 2021. One group including 100 patients were treated with Atorvastatin and the other contains 100 patients were not receiving statin (**Table 1**).

Table 1: Number of cases and controls included in the study.

Study groups	Frequency	Percent %
Atorvastatin Treated	100	50
Non-statin group	100	50
Total	200	100

Targeted population:

This study targeted ischemic heart disease patients with Hyperlipidemia and treated with Atorvastatin for more than two months (Atorvastatin treated group) and ischemic heart disease patients who were not treated with Atorvastatin (Non-statin groups) who were attending National Heart Center in Benghazi between March 2021 and December 2021.

Study design and study sample:

Study design: This study is a single center observational Retrospective cohort study that was conducted at Benghazi National Heart Center (NHC). The study was approved by the research ethics committee, Faculty of Medicine, University of Benghazi.

Sampling design: Participants were selected by random sampling in National Heart Center of Benghazi. The samples were allocated proportionally. Inclusion criteria For Atorvastatin treated group males or females with ischemic heart disease & Hyperlipidemia. Patients were on Atorvastatin tablet 40 or 80 mg/day for more than 2 months. Non-statin Group: males or females with ischemic heart disease. Exclusion criteria for Atorvastatin treated Group & Non-statin treated Group: cases of diabetes mellitus, any patient who was taking medication known to affect blood glucose levels

e.g.; Corticosteroids, Beta-blockers and thiazide diuretics and pregnant females.

Height and weight were measured using a stadiometer and Body Mass Index (BMI): weight in kg divided by height in meters squared (BMI=kg/m^2).

The following lab tests were conducted at National Heart Center laboratory. Venous Blood samples were taken from fasting participants. Serum was separated and the following tests were performed: fasting blood glucose, total cholesterol, triglyceride, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). These tests were performed using FUJIFILM DRI-CHEM NX500 multi-purpose automatic dry-chemistry analyzer. Whereas the glycosylated Hb (HbA1c) test was performed using whole blood samples using G8 Automated Glycohemoglobin Analyzer HLC-723G8.

III. Results:

Age: The average age of both of the groups is almost the same. **Figure 1** shows bar-chart of mean age and standard deviation of the non-statin groups and atorvastatin-treated groups.

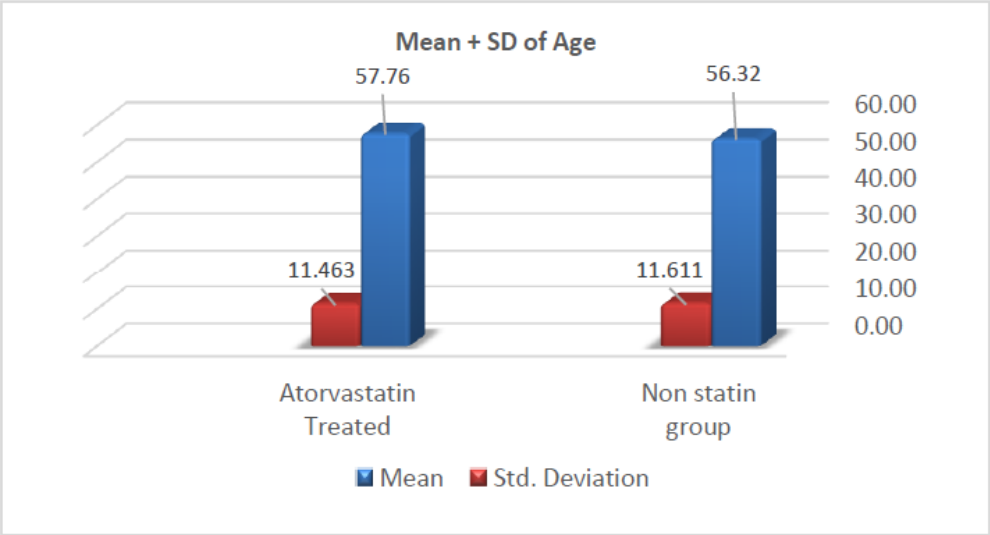

Figure 1: shows mean + SD of age in non-statin groups and Atorvastatin Treated group.

Gender:

The distribution of men and women in both study groups illustrated in **figure 2**. The men count is much higher in both groups. As we see in table 3.5 about 71.5 % of the total participant of study is male and 28.5 is female.

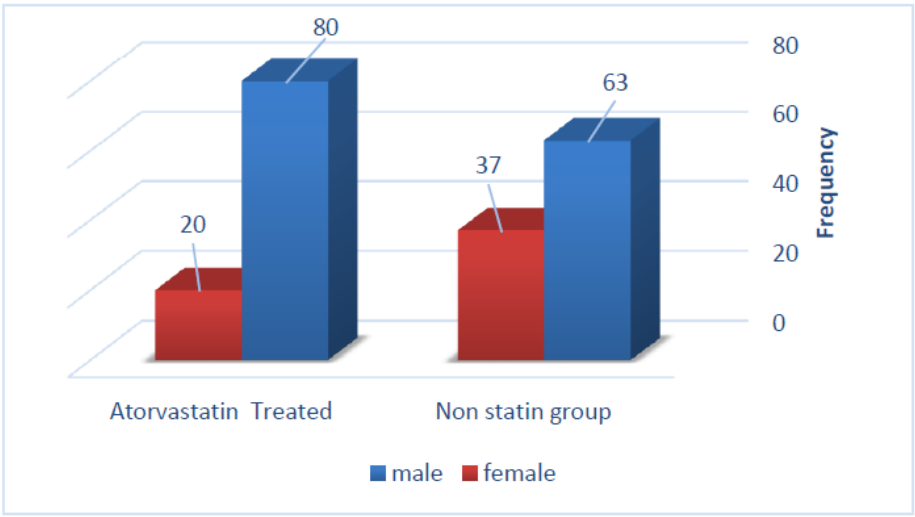

Figure 2: The number of males and females in Non-statin and Atorvastatin Treated groups.

In the present study the male number in control (Non-Statin) Group was (n=63) 44.1%, whereas in atorvastatin treated group was (n=80) 55.9%, female number in control (non-statin) group was (n=37) 64.9%, whereas in atorvastatin treated group was (n=57) 35.1%.

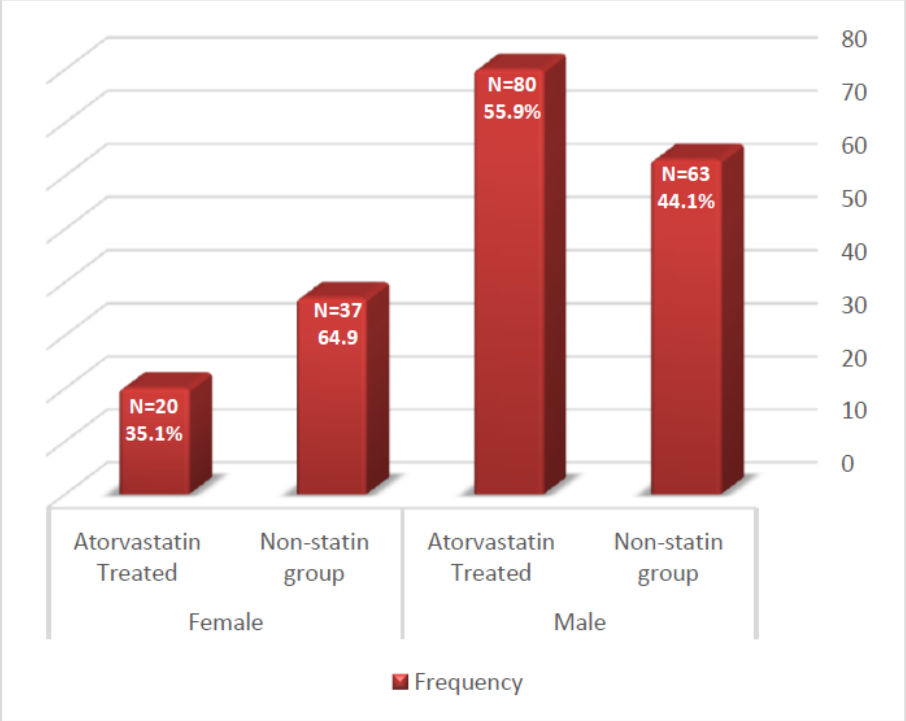

Figure 3.4: Frequency and percentages of male & Female in both of the study Groups.

BMI of both of the study Groups:
The average BMI of both group is almost the same. BMI is about 30 ± 6 (mean ± SD) as illustrated in **figure 5**. Statistical analysis of data revealed that there is any significant difference (P=0.301). between the mean values of BMI in both of the study groups.

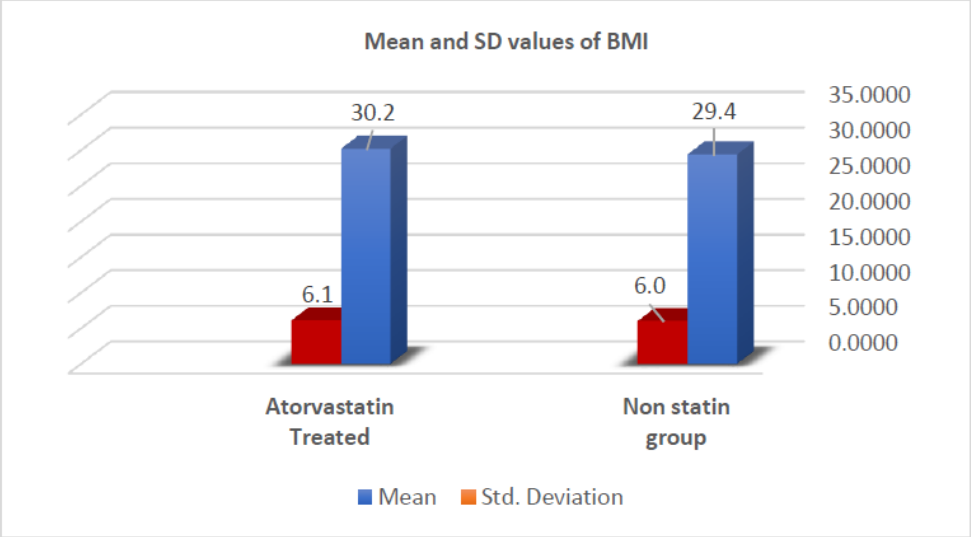

Figure 6: Mean values ± SD of BMI for of both study groups.

Biochemical parameters and lipid profile of both the study groups:
FBG of Atorvastatin treated group; (121.36 ± 24.26) was significantly (P<0.001) higher than the FBG of Non-Statin group (105.43 ± 20.66) as shown in **table 2**.

Table 2: mean, number of cases and standard deviation of all biochemical parametersand lipid profile in Non-statin and Atorvastatin Treated groups .

Biochemical Parameters		Mean ± SD
Non-Statin group (No. of cases 100)	FBG (mg/dL)	105.43 ± 20.66
	HbA1c %	5.524 ± .3836
	S. Cholesterol (mg/dL)	150.97 ± 44.599
	S. Triglyceride (mg/dL)	112.69 ± 50.112
	ALT (U/L)	26.103 ± 14.6042
	AST (U/L)	28.995 ± 16.4251
	FBG (mg/dL)	121.36 ± 24.268
Atorvastatin Treated (No. of cases 100)	HbA1c %	6.096 ± 0.7720
	S. Cholesterol (mg/dL)	158.63 ± 51.266
	S. Triglyceride (mg/dL)	117.30 ± 58.326
	ALT (U/L)	25.101 ± 12.5931
	AST (U/L)	25.552 ± 8.6160

Furthermore, HbA1c% of the Atorvastatin treated group was (6.09% ± 0.77) which was significantly higher than that of control (Non-Statin) Group (5.52 ± 0.38). As clear in **Table 2**: mean ± SD of the biochemical parameters and lipid profile in the study groups.

Results of glycemic control measures: Both FBS and HbA1c showed a high significant increase in Atorvastatin treated group compared to the non-statin group. The other parameters were not significantly different between the study groups (**Figure 7& 8**).

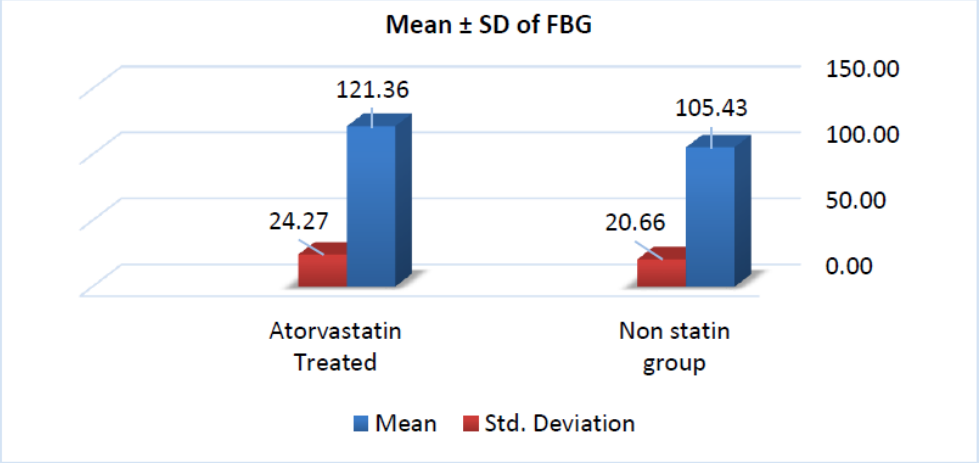

Figure 7: Mean values and SD of FBG for both of the study Groups.

The mean value of FBS (121.36 mg/dl) of the Atorvastatin treated group was high significantly (P<0.001) increased compared to the mean value of FBS (105.43 mg/dl) of the Non-Statin Group (**Figure 7**). In a similar way, the mean value of HbA1c (6.09 %) of the Atorvastatin treated group was high significantly (P<0.001) increased compared to the mean value of HbA1c (5.52 %) of the Non-Statin Group **(Figure 8).**

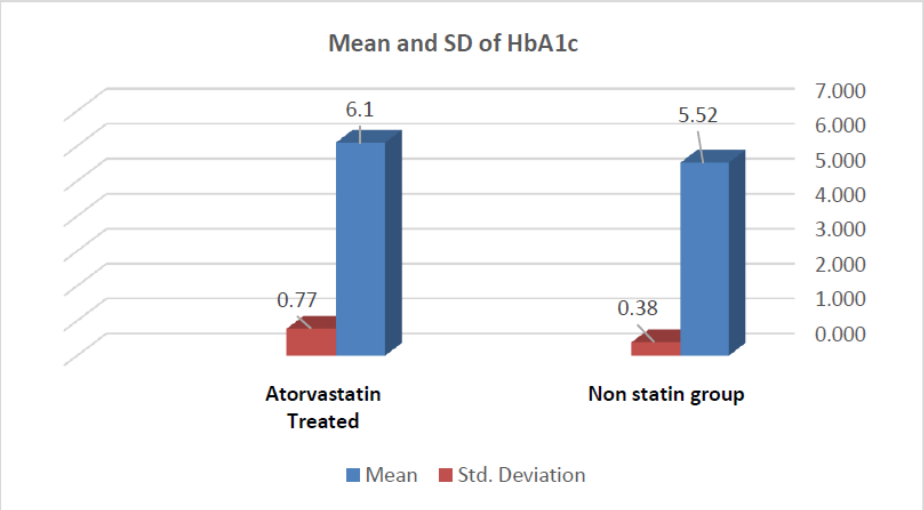

Figure 8: Mean values and SD of HbA1c for both of the study Groups.

The rate of incidence of newly-diagnosed diabetes according to FBG:
The number and percentage of newly-diagnosed diabetics were calculated for both of the study groups. The estimation of diabetic cases was done according criteria of FBG of the American Diabetes Association (FBG level of 126 mg% or more considered as diabetic). Out of 100 cases of Atorvastatin Treated group, 36 cases had newly-diagnosed diabetes, compared to 7 cases in the non-Statin group (**Table 3**).

Table 3: Frequency of newly diagnosed diabetics in the study according to FBG.

Group			Frequency	Percentage
Non-statin group	Valid	Normal	93	93%
		Diabetic	7	7%
Atorvastatin Treated group	Valid	Normal	64	64%
		Diabetic	36	36%

The frequency of newly diagnosed diabetic cases according to HbA1c%:
The number and percentage of newly-diagnosed diabetics were calculated for both of the study groups. The estimation of diabetic cases was done according to the criteria of percentage of HbA1c of the American Diabetes Association (HbA1c level of 6.5% or more considered as diabetic). Out of 100 cases of Atorvastatin Treated group, 25 cases had newly-diagnosed diabetes, compared to zero in the control group (**Table 3**).

Table 4: Frequency of new-onset diabetics in the study according to HbA1c%.

Group		Frequency	Percentage
Non-Statin group	Normal	100	100%
	Diabetic	0	0.0%
Atorvastatin Treated group	Normal	75	75.0%
	Diabetic	25	25.0%

The frequency of newly diagnosed diabetics based on both FBG and HbA1c%:
The number and percentage of newly-diagnosed diabetics were calculated for both of the study groups. The estimation of diabetic cases was done according to the criteria based on the serum levels of FBG and the percentage of HbA1c of the American Diabetes Association (FBG level of 126 mg% or more and HbA1c level of 6.5% or more were considered as diabetic). Out of 100 cases of Atorvastatin Treated group, 17 cases had newly-diagnosed diabetes, compared to zero in the control group (Non-statin) (**Table 5**).

Table 5: Frequency of newly-diagnosed diabetics according to both measures (FBG and HbA1c%).

Group		Frequency	Percentage
Non-statin group	Normal	100	100
	Diabetic	0	0.0
	Total	100	100.0
Atorvastatin Treated group	Normal	83	83.0
	Diabetic	17	17.0
	Total	100	100.0

Correlation between Atorvastatin treatment and the occurrence of new-onset diabetes:
The results of the chi-square test indicate a significant statistical correlation ($P < 0.001$) between taking Atorvastatin and the emergence of new-onset diabetes mellitus (based on FBG, HbA1c or both). Phi Correlation Coefficient show very strong correlation between both of the parameters.

Results of serum lipids:

The mean mg/dl ± SD of Cholesterol levels (158.63 ± 51.26) of Atorvastatin treated group was increased but not significantly compared to that of control (Non-Statin) group was (150.97 ± 44.59). Similarly, Triglycerides levels (117.30 ± 58.32) of Atorvastatin treated group was increased (not significantly) compared to that of control (Non-Statin) group was (112.69 ± 50.11) as clear in **Figure 9.**

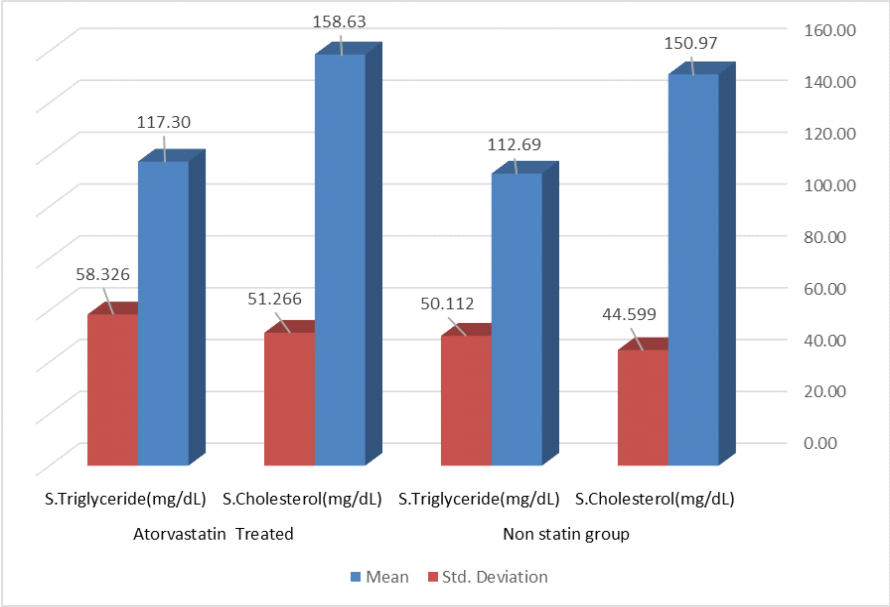

Figure 3.9: Mean value +SD of Cholesterol and TG In both study Groups.

Liver function enzymes:
ALT levels of Atorvastatin treated group (25.1 ± 12.59) was not significantly differ from that of control (Non-Statin) group (26.1 ± 14.60). Similarly, no significant

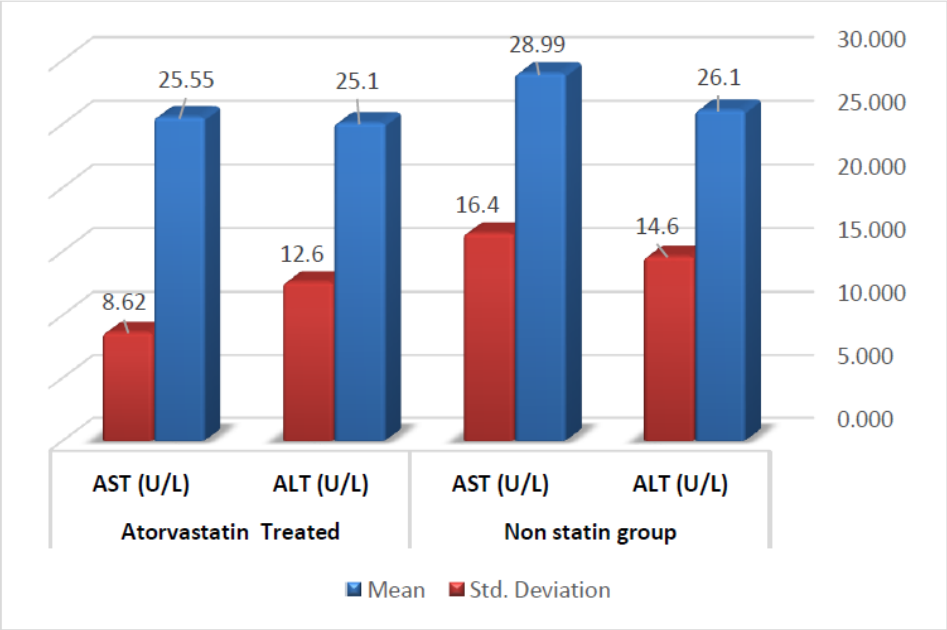

Figure 10: The mean and SD values of ALT and AST of Atorvastatin Treated group and the Non-statin group.

Change was found between the levels of AST of the Atorvastatin treated group (25.55 ± 8.61) and that of control (Non-Statin) group (28.99 ± 16.42).

Classification of the study population based on the dose of statins:
The Atorvastatin-treated subjects were further divided according to the dosage of Atorvastatin used into two categories; Subjects who consumed 40 mg of Atorvastatin per day and Subjects who consumed 80 mg of Atorvastatin per day. We further calculated the number of newly diagnosed diabetic cases (NOD) in both of them using FBG as a diagnostic tool.

- **Subjects who consumed 40 mg of Atorvastatin per day:**

By comparing the mean value of FBG (106.38 mg/dl) of the Non-Statin Group with the mean value of FBG (120.23 mg/dl) of the Atorvastatin 40mg/day treated group, there is a highly significant difference (P<0.001) between FBG in both of the study groups.
Based on the American Diabetes Association criteria of FBG for the diagnosis of diabetes mellitus, we calculated the number of diabetics and we found that; out of 77 participants treated with Atorvastatin 40mg/day, 26 patients had new-onset diabetes, compared to 6 patients in the non-Statin group (**Table 6**).

Table 6: Number NOD in cases in Atrovastatin 40 mg/day and Non-Statin group based on FBG.

Group			Frequency	Percent
Non-statin group	Valid	Normal	71	92.2
		Diabetic	6	7.8
		Total	77	100.0
Atorvastatin Treated (40mg/day)	Valid	Normal	51	66.2
		Diabetic	26	33.8
		Total	77	100.0

- **Subjects who consumed 80 mg of Atorvastatin per day:**

By comparing the mean value of FBG (102.22 mg/dl) of the Non-Statin Group with the mean value of FBG (125.13 mg/dl) of the Atorvastatin 40mg/day treated group, there is a highly significant difference (P<0.001) between FBG in both of the study groups. Based on the American Diabetes Association criteria of FBG for the diagnosis of diabetes mellitus, we calculated the number of diabetics and we found that; out of 23 participants treated with Atorvastatin 80mg/day, 10 patients (43.5%) had new-onset diabetes, compared to 2 patients in the non-Statin group **(Table 7**).

Table 7: Number NOD in cases in Atrovastatin 80 mg/day and Non-Statin group based on FBG.

Group			Frequency	Percent
Non-statin group	Valid	Normal	21	91.3
		diabetic	2	8.7
		Total	23	100.0
Atorvastatin Treated (40mg/day)	Valid	Normal	13	56.5
		diabetic	10	43.5
		Total	23	100.0

IV. Discussion:

In general, statins are used in the treatment of hypercholesterolemia and hypertriglyceridemia both of complications are usual manifestation of overweight and obesity and being overweight, both of these complications are treated with the well-known group of drugs namely statins (Waters et al., 2013). Obesity is also considered an important risk factor for CHD. In turn obesity one of the contributing risk factors for T2D. As we observed in National Heart Center of Benghazi, the most three member of statins used for management of hyperlipidemias in CHD are Atorvastatin *(Ator®)* , Simvastatin *(Zocor®)* and more recently Rosuvastatin *(Crestor®)*, out of those 3 drugs, atorvastatin is always available and cheap, so it is the most frequently used statin drug by Libyan patients.

In 2000, 88,000 diabetics were reported in Libya by WHO. By the year 2030, it was predicted that the prevalence may reach 245,000 diabetics. Based on a national epidemiological research work in 1999, the prevalence for known diabetic patients aged over 20 years was 3.8% (Kadiki and Roaed, 1999). But there is under estimation of the number of diabetics in Libya, because about 50% of type 2 diabetics were did not know about their diabetes (not diagnosed), indicating that the exact prevalence is probably higher (Bakoush and Elgzyri, 2006). In a recent article written by our research group included a summary about recent diabetic classification and the new directions of diabetes treatments. Due to the growing number of diabetics with serious complications which became a major concern for Diabetologists, the author recommended an urgent intervention by health care professionals to improve the overall status diabetic patients (Younis MYG, 2019). Furthermore, diabetes is considered as one of the risk factors that contribute to CHD. Furthermore, Overweight and obesity are among the risk factors for diabetes as well as CHD.

A recent study showed that statins were used for a very long period (>30 years) of time to manage hyperlipidemia associated with CHD. Furthermore, many studies demonstrated that statins reduced the risk for developing atherosclerotic cardiovascular disease (CVD) (Arca 2007, Sadeghi et al., 2014). The drug also used in the management of hypertriglyceridemia linked to diabetes, moreover it has positive role in preventing macrovascular complications associated with diabetes (Chou et al., 2022).

The average age of the participants in current work was 57 years old, ranging from 32 years to 95 years. But the vast majority of individuals aged between 50-69 years old (128 participants) which was younger compared to the participants in studies analyzed in a systematic review (included data from 1.9 million patients) in which the minimum mean age of the participants was 44 and the maximum was 74.9 years (Angelidi et al., 2018).

The number of male participants (143, or 71.5%) is significantly higher than females (57, or 28.5%), This may be in part due to the fact that the prevalence and burden of various CHD vary significantly by gender, for instance, Roger et al., 2011, suggested that the prevalence of CHD was higher in males aged less than 75 years. Whereas, the rate of incidence of CHD in females starts to elevate to become higher than males individuals at 80 years and above (Mosca et al., 2011). Obesity is widely spread among the study participants (WHO/NUT/NCD, 2000); 93 patients were obese (46.5%). Obesity and overweight are among the major risk factors for type 2 diabetes and coronary heart disease. Because the average BMI of both (Atorvastatin treated and Non-statin) groups is almost the same, which neutralize the effect of the abundancy of obesity within both of the study groups. Our findings were in the same line with an early study in Benghazi conducted by Kadiki and Roaed (1999) which showed that 60% of type 2 DM cases were obese. This percentage is comparable to that of developed countries but much higher than the percentages in developing countries.

The effect of statins upon insulin secretion and insulin resistance is not fully understood. Some evidences demonstrated a substantial risk of using statins in the incidence diabetes mellitus (Koh et al., 2010). The later evidence suggested that the risk of developing new onset diabetes risk increased with using of atorvastatin. This finding was in the same line with the results of the present work in which both measures of glycemia (FBG and HBA1c) were significantly increased in Atorvastatin-treated group compared with that of Non-statin control group ($P<0.001$and $P<0.001$, respectively). These findings suggested a role of statin treatment in changing the glycemic control in CHD patients.

The current study showed that individuals receiving atorvastatin medication with both doses (40mg and 80mg) had a considerably greater rate of hyperglycemia and newly diagnosed diabetes than those receiving statin therapy; the incidence of NOD was 36%. Out of 100 patients, 36 patients develop NOD compared with

7% with NOD in the Non-statin group. Our results were in accordance with a study in South Korea in which Koh et al., 2010 studied 213 individuals with hypercholesterolemia were receiving placebo (44 cases) or atorvastatin (43 cases in 40 mg/day, 40 cases in 80 mg/day). They found that fasting insulin and glycated Hb levels elevated significantly in the atorvastatin group after two months of treatment compared to the placebo group, which indicated insulin resistance and higher glycemic level.

In the same line, in India, Nalini et al., 2022, conducted a study including 60 patients on atorvastatin for more than 6 months with normal FBG at the start of therapy. By the end of the study 18 (30%) study patients developed prediabetes and 17 (28%) of them developed NOD (HbA1c was 7.24 ± 0.50). Diabetes incidence was higher among participants with one or more risk factors than among those without a risk factor. This conclusion is also consistent with the present study. Furthermore, A retrospective study included 7064 subjects (755 were statin users and 3928 non-statin subjects). The study includes patients with one or more risk factors for CVD and the others had a CVD event. Zigmont et al., 2019, found that the risk of developing NOD among statin users was 2.2 times greater than non-statin subjects. This is consistent with the current study, which reveals a 5.14 relative risk of developing NOD.

In the contrary to the current study, a retrospective study conducted in Taiwan (from July 2006 to December 2009), Ma et al., found that pravastatin users have a higher chance of developing NOD than outpatients with hypertension and dyslipidemia who take fluvastatin, lovastatin, or rosuvastatin. But surprisingly, simvastatin and atorvastatin had neutral effect (Ma et al.,2012). Furthermore, in South Korea during this year 2022, Seo et al., conducted a retrospective, study including 14,605,368 new users (age $\geq$ 18 years) from 10 hospitals. Seo and colleagues showed that pitavastatin decreased the risk of NOD compared with atorvastatin or rosuvastatin (Seo et al., 2022).

In regard to liver function markers (serum ALT and AST) The mean value of ALT and AST of Atorvastatin treated group showed no significance difference compared to those of the Non-Statin Group. These findings were in disagreement with a previous work of our group in which we found that serum levels of ALT, AST and ALP were significantly increased in both male and female patients following treatment with simvastatin (20mg/day) for 30 days (Roaeid et al., 2016). Similarly, no significant change in the mean serum levels of both total cholesterol and triglycerides in the Atorvastatin treated group compared to those of the Non-Statin Group.

The mechanism underlying the diabetogenic effect of statin treatment is not fully understood. The JUPITER prevention trial, found that using rosuvastatin was associated with elevated C-reactive protein levels (Ridker et al., 2009). In 2015, Swerdlow et al., suggested that increased risk of new-onset DM may be linked to a reduced activity of HMG-CoA reductase. In addition, statin therapy had serious effects on pancreatic β-cells including; decreasing ATP production. Decreasing the activity of K^+ channels and blockage of Ca^{+2} channels which collectively resulted in reduction of exocytosis of insulin vesicles and insulin release.

The lipophilicity of atorvastatin causes diffusion through cell membrane of hepatocellular cells and inhibiting HMG CoA reductase and insulin secretion which in turn potentiates side effects such as increasing prevalence of NOD. Except, pravastatin, which lacks this diabetogenic effect because it is a hydrophilic drug. (Anyanwagu et al, 2016). Furthermore, statins lower the expression of GLUT2 that in turn lowers glucose uptake. and upregulate LDL receptors leading to increase cholesterol uptake which in excess impairs β-cell survival, proliferation, and function leading to death of β-cells (Brault et al., 2014).

Study limitations:

Due to some limitations, the present study did not investigate the mechanisms underlying the diabetogenic effect of statins. This also includes the inability to measure the level of insulin in patients to detect or keep track of insulin resistance. In addition to the above mentioned, the number of study participants is also restricted.

V. Conclusion And Recommendation:

Statins are the golden choice for the prevention of cardiovascular disease. Despite the safety records for these drugs, recent evidences demonstrated side effect of statins on glycemic control. Further research, confirmed alterations of blood glucose levels affected by statin use that in turn increases the frequency of NOD. However, this risk is minor in comparison to the effects of statins in the protection against cardiovascular events. The present study recommends patients particularly on high-dose atorvastatin as well as those at high risk of diabetes, such as the obese and those with metabolic syndrome, should check their blood glucose and glycosylated Hb regularly.

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