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ORIGINAL ARTICLE

The Effect of Atorvastatin Intensity, Obesity, Gender, and Age upon New-onset Type 2 Diabetes Incidence among Libyan Coronary Heart Disease Patients

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Abstract

Background: Atorvastatin is one of the statins family of lipid-lowering drugs. Statin has been linked to protective actions against cardiovascular disease; however, the use of statin has been linked to an increased risk of diabetes.

Aim of the study: To assess the prevalence of diabetes following the use of Atorvastatin and also to evaluate the effect of the statin intensity, BMI, age, and gender upon the glycemic control and incidence of diabetes.

Material and methods: 200 CHD patients divided into 2 groups. The atorvastatin group (using Atorvastatin (40 or 80 mg/day) for<2 months and the control group (non-atorvastatin users). FBG, HbA1c, total cholesterol, triglyceride, ALT, and AST were investigated, and BMI was calculated for all participants.

Results: Generally, the NOD incidence was 17% (17 patients had NOD out of 100 Atorvastatin-consuming patients), whereas, there were no NOD cases in the non-Atorvastatin group (100 cases). The oldest age (≥ 70 years) Atorvastatin-using patients showed the highest incidence of NOD (43.8%). The NOD incidence was higher in the male group with 22 NOD cases (27.5%) than that of the female group which showed 3 NOD cases (15%). Regarding the effect of BMI, the obese group (BMI ≥ 30) showed a higher incidence of NOD (23 cases, 45.1%) than the non-obese group (BMI<30) which showed 13 NOD cases (26.5%) of the atorvastatin using patients. In regards to statin intensity, the 80 mg/day-Atorvastatin subgroup showed 7 NOD cases (30%) which was higher than the 40 mg/day-Atorvastatin subgroup which showed 18 NOD cases (23%) of the atorvastatin using patients.

Conclusion: Atorvastatin treatment was significantly implicated in the development of NOD. NOD incidence increases with higher doses of statin. The risk of NOD was also affected by other factors including; obesity, gender, and old age.

Key Words: *Atorvastatin; Type 2 diabetes; Obesity*

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Introduction

Higher serum cholesterol levels are considered one of the major risk factors for atherosclerosis and cardiovascular diseases (CVD). The lipid profile of CVD patients is usually characterized by elevated low-density lipoprotein cholesterol (LDL-C) and reduced levels of high-density lipoprotein cholesterol (HDL-C) [1]. Another important risk factor for CVD is type 2 diabetes in which hyperlipidemia is usually occurs along with hyperglycemia.

Diabetes is a metabolic disorder, characterized by substantial disturbance of carbohydrate, lipid, and protein metabolism. Obesity is an important risk factor for developing insulin resistance that finally causes diabetes. Uncontrolled diabetics lead to the development of CVD as one of the common pathological complications of the well-known disorder. Diabetes is considered a serious health problem that affects all the populations around the globe. In 2017, the prevalence of the disorder among individuals at the age of twenty to eighty years was 425 million. In 2021, this estimate was further increased to reach 537 million people worldwide. Globally, diabetes not only affects human health but also poses a financial burden on governments worldwide. Life science researchers, drug factories, and healthcare providers are in a race to design novel treatment regimens aiming to cure or at least delay the incidence of various diabetic complications [2,3].

The location of Libya is in the heart of the Middle East region and represents the crown of the North Africa region " MENA". The prevalence of diabetes in this region was 39 million in 2017", this estimate will be doubled by the year 2045. The total number of registered Libyan diabetics was 442.500 which is expected to rise to reach 763.000 by the year 2045. The overall prevalence of diabetes among adults in Libya was 11.2% [4,5]. Statins are the common treatment for hypercholesterolemia as well as hypertriglyceridemia. Statins lower serum cholesterol by competitive inhibition of the key enzyme (3-hydroxy-3-methylglutaryl-coenzyme A; HMG-CoA reductase) [6,7]. No doubt about the great effect of statins in reducing LDL-C, a major causal factor of CVD and atherosclerosis. Statins have also a vital role in the protection against the incidence of CVD and the recurrences of cardiovascular events [8,9].

The data produced by clinical trials provided proof of the safety of statins in the treatment of hyperlipidemia in CVD including diabetics. In addition, these studies indicated that statins had a very low percentage of the incidence of unfavorable vascular events as reviewed by Armitage in 2007 [10]. Statin therapy produces significant reductions in major vascular events irrespective of age, but there is less direct evidence of benefit among patients older than 75 years who do not already have evidence of occlusive vascular disease. However, the most noticeable side effect of statins is the impairment of glycemic control. This adverse effect was supported by the data obtained from the Jupiter study 2008, which reported a high risk of incidence of new-onset diabetes mellitus (NODM) among individuals who were not suffering from CVD when treated with rosuvastatin (20 mg per day) [11]. In a large cohort study, there was a higher risk of insulin resistance (IR) and increased prevalence of NOD [12]. Currently, seven known classes of statins are used to treat hyperlipidemia. Atorvastatin is considered as the most popular type of statins [13]. Little is known about the risk of developing NOD among Libyan patients who are on statin treatment. The current study aims to find out the diabetogenic effects of statins among CVD adult patients in Benghazi, which is the largest province in the eastern part of Libya.

Material and Methods

Population of the study

This is a single-center observational retrospective cohort study carried out at the Benghazi National Heart Center (NHC) from March 2021 to December 2021. The study was approved by the research ethics committee, Faculty of Medicine, University of Benghazi. This work included two hundred patients [143 men (71.5%), 57 women (28.5%)]. They were divided into 2 main groups. The first group (Atorvastatin group) includes CHD patients on Atorvastatin (40 or 80 mg/day) for more than 2 months. The second is the control group (non-Atorvastatin group) includes CHD patients who were not taking any statin medication. This study targeted ischemic heart disease patients with Hyperlipidemia and treated with Atorvastatin for more than two months (Atorvastatin group) and ischemic heart disease patients who were not treated with Atorvastatin (Non- Atorvastatin group). The study subjects were further subdivided based on age, gender, statin dosage, and BMI. FBS and HbA1c were measured for both of the main groups. In addition, the correlation between statin exposure and FBS-HbA1c was measured. Descriptive statistics were also performed.

Statistical analysis

All data collected from the 200 participants were analyzed and presented using three software programs: the Statistical Package for Social Sciences (SPSS) version 26 for Windows, MedCalc version 20 for Windows, and Microsoft Office Excel 2007. Numeric variables were presented as mean and standard deviation (SD), whereas, categorical variables were expressed as numbers and percentages. The mean values of continuous variables were compared in both groups using a Non-parametric Statistical test (Mann-Whitney U) to assess whether the means of FBS and HbA1c were statistically different between Atorvastatin and Non-statin groups. we avoid using parametric tests namely the t-student test because the conditions required to conduct a t-test are not fully met, this includes homogeneity of variance and normal distribution of data [14].

Inclusion and exclusion criteria for the Atorvastatin group and Non-atorvastatin group: 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 at least two months. Exclusion criteria; Non-statin Group: males or females with ischemic heart disease. 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.

Body Mass Index (BMI) was calculated by measuring the height and weight using a stadiometer [weight in kg divided by height in meters squared (BMI=kg/m2)]. Laboratory tests were done at the laboratory of the National Heart Center. Venous blood samples were drawn from fasting participants. The serum was separated and used to perform the following tests: fasting blood glucose (FBG), total cholesterol, triglyceride, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). These tests were performed using a 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.

The aim of the study

The current study aimed to assess the prevalence of NOD following the use of Atorvastatin and

also to assess the effect of the other factors upon the glycemic control and NOD incidence; including the intensity of the statin (40mg/dl and 80mg/dl), BMI index (obese and non-obese individuals), increasing in age (by dividing subjects into different age subgroups and finally the type gender in Atorvastatin treated subjects and the nontreated subjects.

Results

This chapter includes the descriptive statistics of the study population and the statistical analysis of the results of laboratory investigations of study groups (Atorvastatin group and non-atorvastatin group "control") and the further subdivided subgroups.

Age

Table 1 shows the mean age ± standard deviation of the Atorvastatin group (57.8 ± 11.5 years) and non-atorvastatin group (56.2 ± 11.8 years), It is noted that each mean age of both of the groups was very close to the other one.

Moreover, the study subjects were further divided into three subgroups based on age, as shown in Table 2:

(30 – 49 years) Group

(50 – 69 years) Group

(More than 70 years) Group

As clear from (Table 2), the mean age and the number of subjects of every age group is almost the same in both of the 2 main groups (i.e., Atorvastatin and Non-atorvastatin groups).

The results of biochemical tests of the age group 30-49 years

The number of CHD patients in the age range of 30–49 years is 44 patients. Table 3 shows the mean levels ± SD of the biochemical investigation of Atorvastatin and Non-atorvastatin groups. The mean value of Blood glucose (102.38 mg/dl) of the non-atorvastatin group was significantly lower (P=0.024) than that (118.25 mg/dl) of the Atorvastatin group. Similarly, the mean HbA1c (5.53%) of the non-Atorvastatin group was significantly lower (P=0.007) than the HbA1c levels (5.97%) of the Atorvastatin group. Alternatively, the serum levels of cholesterol, TAG, ALT, and AST were non-significantly (P>0.05) changed in the Atorvastatin group compared to the non-atorvastatin group.

The incidence of NOD among the age group 30–49 years

As shown in Table 4, among the age group 30–49 years, the incidence of NOD on the basis of HbA1c, was 10% in the Atrovastatin group whereas there was no any NOD case in the non-Atorvastatin group.

TABLE 1
Mean +SD of age in the atorvastatin group and non-atorvastatin group

	Atorvastatin group		Non-atorvastatin group
N	Mean ± SD years	N	Mean ± SD years
100	57.76 ± 11.46	100	56.23 ± 11.8

TABLE 2
Shows the mean age ± SD in years of the 3 age subgroups of the study

Study Groups	30-49 years Mean ± SD	No.	50-69 years Mean ± SD	No.	≥ 70 years Mean ± SD	No.
Non-atorvastatin	42.04 ± 5.2	24	57.67 ± 4.77	64	76.63 ± 7.85	16
Atorvastatin	42.00 ± 4.7	20	58.03 ± 5.34	64	76.38 ± 4.27	16

TABLE 3
The results of the biochemical tests of the 50–69 years age group

Biochemical Parameters	Atorvastatin group (N= 20)	Non- Atorvastatin (N= 24) Group	P value
FBG (mg/dl)	118.3 ± 33.6	102.4 ± 14	(P < 0.05)*
HbA1c (%)	5.98 ± 0.8	5.5 ± 0.3	(P < 0.05)*
Chol. (mg/dl)	157.5 ± 49.6	153 ± 33	(P > 0.05)
TAG (mg/dl)	107.7 ± 32.9	106.2 ± 43.9	(P > 0.05)
ALT (U/l)	31.1 ± 20.75	25.44 ± 16.4	(P > 0.05)
AST (U/l)	27.1 ± 8.9	33 ± 26.4	(P > 0.05)

TABLE 4
The number of NOD cases (based on HbA1c levels) in among the age group 30–49 years

Groups	Normal	Diabetic
Atorvastatin	18	2 (10%)
Non-Atorvastatin	24	0 (0 %)

The results of biochemical tests of the age group 50-69 years

There were 128 CHD patients in the age group (50–69 years). Table 5, shows the mean ± SD of the biochemical tests. The mean value of Blood glucose of the Atorvastatin group was 123 ± 23 mg/dl which was significantly (P<0.0001) higher than the blood glucose levels (108.3 ± 22.3 mg/dl) of the non-Atorvastatin group. Similarly, the mean level of HbA1c% (6.15 ± 0.8%) of the Atorvastatin group was significantly (P<0.0001) higher than the mean HbA1c (5.52%) of the non-atorvastatin Group. Cholesterol, TAG, ALT, and AST were unchanged (P>0.05) in the Atorvastatin group compared to the non-atorvastatin group.

The incidence of NOD among the age group 50–69 years

In the 50–69 years age group, the incidence of NOD (based on HbA1c) was 12.5% in the Atorvastatin group (N= 64 CHD patients) whereas there were no NOD cases in the non-atorvastatin group (N= 64 CHD patients) as shown in Table 6.

TABLE 5
The means ± SD of the biochemical tests of the 50–69 years age group

Biochemical Parameters	Atorvastatin group (N= 64)	Non-Atorvastatin group (N= 64)	P Value
FBG (mg/dl)	123 ± 23	108.3 ± 22.3	(P < 0.0001)*
HbA1c (%)	6.15 ± 0.8	5.52 ± 0.4	(P < 0.0001)*
S. Chol. (mg/dl)	157.4 ± 51.95	148 ± 47.2	(P > 0.05)
TAG (mg/dl)	122.7 ± 68	118.5 ± 55	(P > 0.05)
ALT (U/l)	23.9 ± 9.2	27 ± 14.6	(P > 0.05)
AST (U/l)	25 ± 8.5	29.6 ±16.94	(P > 0.05)

TABLE 6
The number of NOD cases among age group (50–69 years)

Groups	Normal	Diabetic
Non-statin Group	64	0 (0.00 %)
Atorvastatin Group	56	8 (12.5 %)

The results of biochemical tests of the age group (equal to or>70 years)

There were 32 CHD patients within the age group 70 years or more, which were further divided into 2 main groups (Atorvastatin and non-atorvastatin groups). The mean level of FBS (120 ± 17 mg/dl) of the atorvastatin-treated group was significantly (P<0.05) higher than the mean level of FBG (101 ± 20 mg/dl) of the non-atorvastatin group as shown in Table 7. Similarly, the mean level of HbA1c (6.2 ± 0.5%) of the Atorvastatin group, was significantly (P<0.05) increased compared to the mean value of HbA1c (5.5 ± 0.5%) of the non-Atorvastatin group. Alternatively, the serum cholesterol, TAG, ALT, and AST were non-significantly (P>0.05) changed in the Atorvastatin group compared to the non-atorvastatin group.

The incidence of NOD among the age group 70 years or more

In the ≥ 70 years age group which contains a total of 32 participants, the incidence of NOD (based on HbA1c levels) in the Atorvastatin group was very high (43.8%) compared to 6.3% of NOD cases in the non-Atorvastatin group, as shown in Table 8.

Distribution of study population based on gender

As shown in Table 9, about 71.5% of the total participants of the study were males (N=143 subjects), Moreover, their mean age was 55.99 ± 10.1 years, and the mean BMI was 29.4 ± 5.5. The number of females (N=57 subjects) with a percentage of 28.5 of the total study population and their mean age was 59.7 ± 14.2 years and the BMI was 30.75 ± 7.3.

Biochemical tests in the male group

There were 143 CHD male patients (Table 10). The mean level of FBG of the Atorvastatin group was 122.4 ± 26.3 mg/dl which is significantly (P<0.001) higher than FBG (108.3 ± 22.3 mg/dl) of the non-Atorvastatin group. Similarly, the mean level of HbA1c% (6.15 ± 0.84) of the Atorvastatin group was significantly (P<0.001) higher than the mean HbA1c (5.5 ± 0.4%) of the non-Atorvastatin group. The serum cholesterol, TAG, ALT, and AST were changed (P>0.05) in both groups.

TABLE 7
The means ± SD of the biochemical tests of the age group 70 years or more

Biochemical parameters	Atorvastatin group (N= 64)	Non-Atorvastatin (N=64) group	P value
FBG (mg/dl)	120 ± 17	101 ± 20	(P < 0.05)*
HbA1c (%)	6.2 ± 0.5	5.5 ± 0.5	(P < 0.05)*
Chol (mg/dl)	164.8 ± 53.4	163 ± 49.3	(P > 0.05)
TAG (mg/dl)	108 ± 36.1	97.4 ± 30.1	(P > 0.05)
ALT (U/l)	22.6 ± 9.4	24.4 ± 12	(P > 0.05)
AST (U/l)	26 ± 9.1	31.3 ± 21	(P > 0.05)

TABLE 8
The number of newly diagnosed diabetics (NOD) among ≥70 years age group

Group	Normal	Diabetic (NOD)
Atorvastatin	12 (56.3%)	4 (43.8%)
Non-Atorvastatin	15 (93.8)	1 (6.3%)

TABLE 9
Age, BMI, and number and percentages of males and females among the study participants

Gender	Number of cases and %	Age (years) Mean ± SD	Body mass index BMI Mean ± SD
Males	143 (71.5%)	55.99 ± 10.1	29.4 ± 5.5
Females	57 (28.5)	59.7 ± 14.2	30.75 ± 7.3

TABLE 10
Shows the results of the biochemical tests of the male groups

Biochemical Parameters	Atorvastatin (N= 80, 56%)	Non- Atorvastatin (N= 63, 44%)	P value
FBS (mg/dl)	122.4 ± 26.3	105.8 ± 19.5	(P < 0.001)*
HbA1c %	6.15 ± 0.84	5.51± 0.41	(P < 0.001)*
Chol. (mg/dl)	160.1 ± 53.7	156.6 ± 47.1	(P > 0.05)
TAG (mg/dl)	116.3 ± 56.9	121.3 ± 14.6	(P > 0.05)
ALT (U/l)	26.5 ± 13.3	27.7 ± 14.6	(P > 0.05)
AST (U/l)	26.5 ± 8.5	30.5 ± 17.9	(P > 0.05)

The incidence of NOD among the male subjects of the study

The incidence of NOD among the male group (143 patients) was high with 22 NOD cases (27.5%) out of 80 subjects. Whereas, the the non-Atorvastatin "male" group (N=63 subjects) showed no NOD cases as shown in Table 11.

Biochemical tests in the female group

There were 57 CHD female patients included in this work (Table 12). The mean level of blood glucose of the Atorvastatin group was 117.2 ± 12.9 mg/dl which is significantly (P<0.01) higher than the mean blood glucose (108.3 ± 22.3 mg/dl) of the non-Atorvastatin group. Similarly, the mean level of HbA1c% (6.1 ± 0.4) of the Atorvastatin group was significantly (P<0.0001) higher than the mean HbA1c (5.6 ± 0.33) of the non-Atorvastatin group. On the other hand, the serum cholesterol, TAG, ALT, and AST were non-significantly (P>0.05) changed in the Atorvastatin group compared to those of the non-atorvastatin group.

The incidence of NOD among the female subjects of the study

The female gender group included 121 participants, and the incidence of NOD (based on HbA1c levels) in Atrovastatin "male" group was high with 22 NOD cases (43.8%) and 58 nondiabetics out of 80 subjects. Whereas, the the non-Atorvastatin "male" group (N=63 subjects) showed no NOD cases as shown in Table 13.

TABLE 11
The incidence of NOD among the male subjects of the study

Study groups	Number and percentages of NOD cases in Males		Total No. of cases
	Normal	NOD	
Atorvastatin	58 (72.5%)	22 (27.5%)	80
Non-Atorvastatin	63 (100%)	0 (0%)	63

TABLE 12
Shows the results of the biochemical tests of the female groups

Biochemical Parameters	Atorvastatin (N=20 35.1)	Non-Atorvastatin (N=37, 64.9%)	P value
FBG (mg/dl)	117.2 ± 12.9	104.9 ± 22.8	(P < 0.01)*
HbA1c %	6.1 ± 0.4	5.6 ± 0.33	(P < 0.001)*
Chol. (mg/dl)	152.8 ± 40.6	141.3 ± 38.73	(P > 0.05)
TAG (mg/dl)	121.3 ± 65.3	98.05 ± 38.8	(P > 0.05)
ALT (U/l)	19.7 ± 7.3	23.3 ± 14.4	(P > 0.05)
AST (U/l)	21.8 ± 8.1	26.5 ± 13.4	(P > 0.05)

TABLE 13
The incidence of NOD among the female subjects of the study

Study groups	Number and percentages of NOD cases in Females		Total No. of cases
	Normal	NOD	
Atorvastatin	17 (85%)	3 (15%)	20
Non-Atorvastatin	37 (100%)	0 (0%)	37
Total numbers	54	3	57

Basal Metabolic Index (BMI)

The obesity status of the entire study population based on BMI values is presented in (Figure 1). This helps us understand just how pervasive obesity is in our culture. In the current work, about 46.5% of study participants were obese Moreover, more than a third (33%) of the participants were overweight, whereas, one-fifth (20%) of the participants had normal weight and only 1 subject (0.5%) was underweighted.

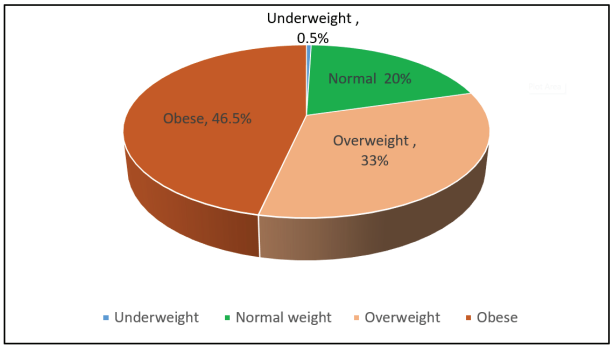

Figure 1) *Showed the percentages of BMI values of all the 200 study subjects.*

The BMI of the main study groups

The average BMI ± SD of the Atorvastatin group was 30.2 ± 6.1 and the BMI of the non-atorvastatin group was 29.4 ± 6.03. Both of the BMI values were almost the same. Moreover, there was no significant (p=0.301) difference between the BMI values of the main study groups.

The study participants were sub-grouped into non-obese and obese

To study the effect of BMI (obesity) on statin diabetogenicity, we further divided the whole study population (N= 200 subjects) into obese subjects (N=93 subjects, BMI ≥ 30) and non-obese (N=107 subjects, BMI<30) groups).

The results of biochemical investigations of the non-obese subjects (BMI<30)

As illustrated in Table 14, the blood glucose (117.9 ± 20.9 mg/dl) of the Atorvastatin group was highly significant (P<0.001) increased compared to the mean blood glucose level (105.6 ± 20 mg/dl) of the non-Atorvastatin group of non-obese subjects. In accordance, the mean value of HbA1c% (6.1 ± 0.9%) of the Atorvastatin group was significantly (P<0.001) higher than the mean value of HbA1c% (5.5 ± 0.41%) of the non-Atorvastatin group. Meanwhile, the mean serum cholesterol, TAG, ALT, and AST values were non-significantly (P>0.05) changed in the Atorvastatin group compared to the non-atorvastatin group.

The incidence of NOD in the non-obese subjects (BMI<30)

In (Table 15) we calculate the number and percentage of diabetics (NOD) in both groups of non-obese patients. For the diagnosis of diabetes mellitus, we relied on the American Diabetes Association criteria (FBG more than 126 mg/dl). Out of 49 participants in the Atorvastatin group, 13 patients had new-onset diabetes, compared to 4 patients in the non-atorvastatin group.

The results of biochemical investigations of the obese subjects (BMI ≥ 30)

The present work found a high significant (P<0.001) difference of the fasting blood glucose (mean ± SD) 124.7 ± 26.9 mg/dl of the Atorvastatin group and the mean level of FBG 105.3 ± 21.8 mg/dl of the non-Atorvastatin group (Table 16). In a similar vein, the mean value of HbA1c 6.12 ± 0.63% of the Atorvastatin group was significantly (P<0.001) higher than the mean value of HbA1c 5.56 ± 0.35% of the non-Atorvastatin group. Alternatively, the s. cholesterol, TAG, ALT and AST were non-significantly (P>0.05) changed in Atorvastatin group compared to non-Atorvastatin group.

TABLE 14
Shows the results of the biochemical tests of the non-obese subjects (BMI < 30)

Biochemical Parameters	Atorvastatin group (N= 49)	non-Atorvastatin group (N= 58)	P value
FBG (mg/dl)	117.9 ± 20.9	105.6 ± 20	(P < 0.001)*
HbA1c (%)	6.1 ± 0.9	5.5 ± 0.41	(P < 0.05)*
Chol (mg/dl)	158.4 ± 44.6	159.30 ± 47.74	(P > 0.05)
TAG (mg/dl)	121.4 ± 70.1	114.4 ± 53.1	(P > 0.05)
ALT (U/l)	25.1 ± 9.73	27.7± 17	(P > 0.05)
AST (U/l)	26.3 ± 9.52	30.27 ± 17.84	(P > 0.05)

TABLE 15
Shows the number of NOD cases of the non-obese (BMI < 30) cases

Groups with BMI < 30	Normal	Diabetic (NOD)
Atorvastatin group	36 (73.5%)	13 (26.5%)
Non atorvastatin group	54 (93.1%)	4 (6.9%)

TABLE 16
Shows the results of the biochemical investigations of the obese subjects (BMI ≥ 30)

Biochemical Parameters	Atorvastatin (N= 51)	Non-Atorvastatin group (N= 42)
FBG (mg/dl)	124.7 ± 26.9	105.3 ± 21.8
HbA1c (%)	6.12 ± 0.63	5.56 ± 0.35
Chol.	158.86 ± 57.397	139.45 ± 37.424
TAG (mg/dL)	113.41 ± 44.637	110.31 ± 46.261
ALT (U/L)	25.143 ± 14.9382	23.933 ± 10.2427
AST (U/L)	24.851 ± 7.6835	27.238 ± 14.2620

The incidence of NOD in the obese subjects (BMI ≥ 30)

In (Table 17), we calculated the number and percentage of diabetics in the main groups for the obese subjects. For the diagnosis of diabetes mellitus, we relied on the American Diabetes Association criteria of FBG. Out of 51 participants in the Atorvastatin group, 23 (45.1%) patients had new-onset diabetes, compared to 3 (7.1%) patients out of 42 subjects of the non-Atorvastatin group.

FBG and HbA1c of the 40 or 80 mg/day Atorvastatin subgroups

The mean blood glucose level (120 ± 23.6 mg/dl) and the mean HbA1c (6.1 ± 0.8%) of the Atorva-40 mg/day subgroup, were significantly (P<0.001) increased compared with those of the non-Atorvastatin group (106 ± 21.4 mg/dl and 5.5 ± 0.4%, respectively). Whereas, the average blood glucose values (125 ± 26.7 mg/dl) and the average HbA1c (6.1 ± 0.72%) of the Atorva-80 mg/day subgroup, were significantly (P<0.001, P<0.05) increased compared with those of the non-Atorvastatin group (102 mg/dl ± 14.3 and 5.6 ± 0.33%, respectively).

The prevalence of NOD among 40 mg/day and 80 mg/day Atorvastatin subgroups

The effects of 40 mg/day Atorvastatin drugs on the glycemic status were achieved by assessing the frequency of NOD based on the levels of HbA1c%>6.5%, as illustrated in Table 18. Out of 77 subjects in the 40 mg/day-Atorvastatin subgroup, 18 patients (23%) had NOD, whereas there was no NOD case among 77 in the non-Atorvastatin group. Similarly, 7 patients (30%) had NOD out of 23 subjects in the 80 mg/day-Atorvastatin subgroup, whereas there were no NOD cases among the 23 subjects of the non-Atorvastatin group.

Correlation between Atorvastatin dose; 40 or 80 mg/day and NOD incidence

By using the chi-square test and Phi correlation coefficient, the results indicated a strong significant positive correlation between taking Atorvastatin 40 mg or 80 mg per day (P<0.001 and (P<0.05) and the emergence of new-onset diabetes mellitus (NODM).

Laboratory investigation of the whole No. (200) of the study subjects

The blood glucose level (121 ± 24.3 mg/dl) of the Atorvastatin group was significantly (P<0.001) high compared to that (105 ± 20.7 mg/dl) of the non-atorvastatin group. Similarly, as clear from (Table 19) the HbA1c level (6.1 ± 0.8%) of the Atorvastatin group was significantly (P<0.001) high compared to that (5.5 ± 0.4%) of the non-Atorvastatin group. These findings indicate a significant effect of statin treatment on the glycemic status of the study population. On the other hand, the comparison of the mean values of serum lipids (cholesterol and triglycerides) and liver enzymes (ALT and AST) in both of the main study groups, showed no significant difference as appeared in (Table 19).

TABLE 17
Shows the number of NOD cases of the non-obese (BMI ≥ 30) cases

Groups with BMI ≥ 30	Normal	Diabetic
Atorvastatin (N= 51)	28 (54.9%)	23 (45.1%)
Non-Atorvastatin (N=42)	39 (92.9%)	3 (7.1%)

TABLE 18
Number of NOD in both subgroups of Atorvastatin dosages (40 and 80 mg/day)

Study Subgroups	Number (%) of NOD for Atorva-40 mg/day		Number (%) of NOD for Atorva-80 mg/day	
	Normal	NOD	Normal	NOD
Atorvastatin	59 (77%)	18 (23%)	16 (70%)	7 (30%)
Non-Atorvastatin	77 (100%)	0	23(100%)	0

TABLE 19
Shows the mean ± SD of the biochemical tests of the main study groups

Laboratory tests	Atorvastatin Group (N=100)	Non-Atorvastatin Group (N=100)	P value
Glucose (mg/dl)	121 ± 24.3	105 ± 20.7	P < 0.001*
HbA1c %	6.1 ± 0.8	5.5 ± 0.4	P < 0.001*
Chol. (mg/dl)	159 ± 51.3	151 ± 44.6	P > 0.050
TAG (mg/dl)	117 ± 58.4	113 ± 50.1	P > 0.050
ALT (U/l)	25 ± 12.6	26 ± 14.6	P = 0.773
AST (U/l)	26 ± 8.6	29 ± 16.4	P = 0.726

The effects of Atorvastatin drug on the glycemic control of the study population

The influence of Atorvastatin drugs on the glycemic status was achieved by assessing the frequency of newly diagnosed diabetics (New-onset diabetes, NOD) based on both FBG and HbA1c% (Figure 2). According to the criteria of the American Diabetes Association diabetic cases were diagnosed when serum FBG values were>126 mg% and the blood HbA1c levels were>6.5%. Out of 100 Atorvastatin-consuming patients, 17 patients had NOD, whereas, there were no NOD cases in the non-Atorvastatin group.

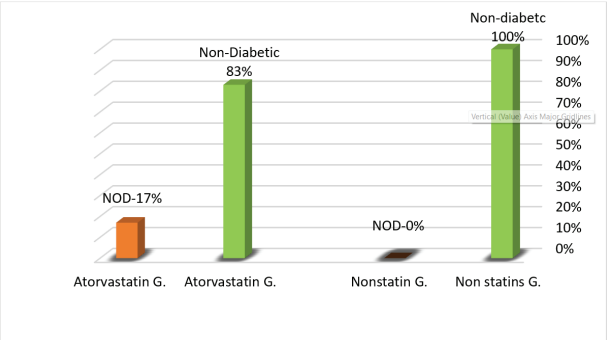

Figure 2) *Number of new-onset diabetic in the study population (200 subjects) based on FBG and HbA1c levels.*

Discussion

It is more than one-third of a century since the introduction of the first statin drug, many clinical trials concluded that statins were effective in reducing the risk of atherosclerosis and CVD events even in patients living with diabetes [15]. Statins relieve hypercholesterolemia by reducing serum levels of low-density lipoprotein cholesterol (LDL-C) levels, which is known as "the bad cholesterol", statins also are effective as a treatment of hypertriglyceridemia. However, large clinical trials demonstrated that the use of statins increases the risk of having diabetes (New-onset diabetes), such as the JUPITER trial treated 17,802 individuals and reported a high prevalence of diabetes in the rosuvastatin group compared to the placebo-treated control group.

On the other hand, A meta-analysis was conducted in 2010 on 13 placebo or standard-care RCT statin trials. The study involved 91,140 participants, out of which 2.44% who received statins developed DM (2226 cases) as compared to 2.25% (2052 cases) who received placebo over an average of 4 years. The research found that statin therapy increased the risk of incident DM by 9% (OR 1.09, 95% CI 1.02Y1.17), with a higher risk among older adults. The efficacy of the statin on lipid values and body mass index (BMI) did not affect the results. When statins were used for primary prevention, there was a lower risk of incident DM than those used for secondary prevention. Trials that had the highest incidence of DM included participants with known risk factors for DM such as heart failure, MI within the last 6 months, elderly adults, or those at high risk of CV disease. The authors concluded that treating 255 patients with statin therapy for 4 years would result in 1 additional case of DM [16].

In Libya, a previous work of Kadiki and Roaed in 1999 [17], conducted a national epidemiological research study and reported a prevalence of 3.8% of diabetes among individuals aged ≥ 20 years. In 2000, the WHO work in Libya reported a total number of 88,000 diabetics. The prevalence was predicted to reach the edge of 245,000 diabetics in 2030. However, the diabetic records were underestimated in Libya, because about half of type 2 diabetic Libyan patients did not know about their diabetes (not diagnosed), indicating that the actual prevalence of the disease is much higher than the announced numbers as reported by Bakoush and Elgzyri in 2006 [18]. Due to the growing number of diabetics and the higher risk of increasing the serious complications of the disease, the author of this paper encourages an official intervention by healthcare professionals to improve the current status of all diabetics and also to help the people who are at higher risk (prediabetics) to avoid having diabetes.

The effects of Atorvastatin on the prevalence of NOD in age sub-groups of the study population

The mean age of the subjects in the present study was about 57 years (age range 32-95 years). The study subjects were further grouped into 3 categories 30 – 49 years, 50 – 69 years and more than 70 years old subjects. However, most of the study participants aged between 50-69 years old (128 participants) which was younger than the age range in a group of studies in a systematic review (included data of 1.9 million patients) in which the age range was 44 to 74.9 years [19].

In the current study, the highest NOD prevalence in the Atorvastatin group among the age group ≥ 70 years old was 4 NOD cases out of 16 cases with a percentage of 43.8%. Regarding the age group 50–69 years (N=128 subjects), the prevalence of NOD was 12.5% of the atorvastatin-treated patients (N=64 CHD patients), whereas the NOD cases of the age group 30 – 49 years were 2 cases out of 20 cases (10%). On the other hand, there were no NOD cases reported in the non-atorvastatin group. These results indicated that the incidence of diabetes was increasing with increasing age. However, our data showed a limitation concerning the number of subjects in the younger adult and the old age group with 20 and 16 subjects, respectively.

Our results were in agreement with Caspersen and his colleagues in 2012, who suggested that aging is a risk factor for developing diabetes [20]. Furthermore, the current data were in agreement with a recent study by Fazeli et al., 2020, who reported that the influence of aging is clearly observed after the age of 40 years [21]. The author also concluded that as a consequence of getting old, non-obese people who are >70 have the same risk of acquiring type 2 diabetes as those in their 30s with a higher BMI (obese BMI range), which indicated that aging is a very strong risk factor for acquiring diabetes regardless the BMI values. This conclusion could explain why the incidence of NOD in the present study, was gradually rising with increasing age. In agreement with our findings, Zafrir and Jain 2014 suggested that older subjects who suffer from metabolic syndrome and who had impaired glucose tolerance before starting statin treatment had a higher risk of developing diabetes [22,23]. Furthermore, our findings were on the same line with Trias et al., 2022 who conducted an observational study included 407 in older prediabetics (mean age 63.1 ± 11years) treated with Atorvastatin and found that the diabetogenic effect increased with due to an impaired glucose metabolism.

The influence of Atorvastatin on biochemical parameters of both genders

In our work, it is noted that the number of men (143, 71.5% of total subjects) was markedly higher than women (57, 28.5%). This could be explained partly in the light of the fact that the CHD prevalence and burden vary depending on gender. Previous work suggested that men aged<75 years had a higher prevalence rate of CHD [24]. On the other hand, Mosca and colleagues 2011, suggested that women started to have a higher prevalence of CHD than men at the age of ≥ 80 years [25].

The mean level of blood glucose and HbA1c% of the Atorvastatin male group was significantly (P<0.001) higher than those of the non-atorvastatin male group. Moreover, the prevalence of NOD (based on HbA1c levels) in Atrovastatin "male" group was high with 22 NOD cases out of 80 subjects (27.5%). Our work was in agreement with a retrospective cohort study conducted in Taiwan and included male subjects from July 2004 to December 2009.

This study has diagnosed a total of 2735 NOD (17.5%) subjects out of 15,637 hypertensive and dyslipidaemic old adult patients with a prevalence rate of 17.5% [26].

The risk of NOD (27.5%) in atorvastatin-treated males in the current work was lower than the risk of NOD (46%) reported in The METSIM cohort study. This is a valuable study focused on the association of metabolic syndrome and statin-induced diabetes in 8749 males (non-diabetics at the baseline, aged 45 to 73 years) treated with various statins for six years. The higher risk of NOD in statin users was accompanied by a 12% decrease in insulin secretion and a 24% reduction in insulin sensitivity. A significant influence on these parameters was observed in subjects treated with atorvastatin and simvastatin [27].

In the present study, the NOD prevalence (27.5%) among Atorvastatin-treated males where higher than the females (3 NOD cases out of 20 female cases, 15%). On the other hand, a previous study showed that the risk of NOD was very high among females. The Women's Health Initiative tested the effect of different types of statins on 161,808 postmenopausal women (non-diabetics at baseline). This study showed that the risk of NOD was increased with the use of statins and Atorvastatin in particular was associated with a 48% increased risk of NOD [28]. Another clinical trial, conducted in Finland, included 28 females (aged 29–50 years) with polycystic ovary syndrome, they were treated with 20mg of Atorvastatin for 6 months and had no diabetes at the baseline. The FBG levels (5.5 ± 0.4 mmol/l) were significantly (p=0.007) increased compared with control (5.0 ± 0.5 mmol/l) who consumed a placebo for the same period which indicated that Atorvastatin had deteriorated the glycemic control of those women [29].

The effects of Atorvastatin on the prevalence of NOD in dosage sub-groups (40 and 80 mg/day) of the study population

The present study investigated the diabetogenic effects of Atorvastatin doses (40 and 80 mg/day). Statin intensity is defined as which statin dosage can reduce the levels of LDL-C, thus statins are grouped into 3 categories; low, moderate, and high-intensity. This classification is used by clinicians to prescribe statins to prevent CVD [30]. The high-intensity statins (reduce LDL-C levels by at least 50%) include Atorvastatin (40–80 mg) and Rosuvastatin (20–40 mg). Moreover, in the PROVE-IT TIMI 22 sub-study (2009), Gibson et al., demonstrated that intensive treatment with 80 mg/day of atorvastatin leads to lowered major adverse cardiovascular events in patients suffering from acute coronary syndrome compared with moderate-dose (40mg/day) statin treatment. This outcome was achieved via lowering LDL-C levels from 107mg/dl at baseline to 56.5mg/dl ($p < 0.001$) following atorvastatin (80mg/day) for one month [31]. The present work showed that receiving Atorvastatin (80mg/day) had a greater (30%) rate of incidence of new-onset diabetes compared to 23% for Atorvastatin (40mg/day) which indicated that the incidence of NOD is dose-dependent. The present study also used the chi-square test and Phi correlation coefficient, which indicated a strong significant positive correlation between taking Atorvastatin 40 mg or 80 mg per day ($P<0.001$ and $P<0.05$, respectively) and the emergence of new-onset diabetes mellitus (NODM). The current study following [23], who found that patients received atorvastatin 40–80 mg/day showed higher HbA1c levels than those who received atorvastatin 10–20 mg/day (p=0.003) or pitavastatin 1–4 mg/day (p=0.016). Our work was also agreed with another study which analyzed high and Low

doses of statins compared with the controls who received placebo. In a meta-analysis, Sattar and colleagues in 2010 [16], estimated the overall odds ratios for incident diabetes and found that it was elevated with rosuvastatin (1.18), atorvastatin (1.14), and simvastatin (1.11) than with pravastatin (1.03) and lovastatin (0.98).

On the contrary, a retrospective cohort study has found that Atorvastatin did not affect the incidence of new-onset diabetes [32]. Another work by Angelidi et al., in 2018 found that not only does Atorvastatin not elevate the risk of diabetes but also may have a protective effect for elderly hypertensive and dyslipidemic patients. In addition, in 2001, the first study focused on the possible link between statin usage and new-onset type 2 diabetes; was the West of Scotland Coronary Prevention Study (WOSCOPS) by Freeman et al., 2001, which was a primary prevention statin trial [33]. The study demonstrated that pravastatin treatment reduced the risk of developing type 2 diabetes by 30%. This effect may be due to the triglyceride-reducing action and the anti-inflammatory effects of pravastatin, in the long term may reduce the risk of insulin resistance which in turn reduces the prevalence of type 2 diabetes [34].

The effects of Atorvastatin on the prevalence of NOD *mong the study population grouped according to BMI:

In our study, the incidence of NOD in the obese subjects (BMI ≥ 30 kg/m2) consuming Atorvastatin was 23 Out of 51 patients (45.1%) compared to 26.5% (23 NOD cases Out of 49 patients) in the subjects consuming Atorvastatin with BMI<30 kg/m2. These findings showed a substantial effect of higher values of BMI on the incidence of NOD among the study subjects. Our findings were in accordance with Kohli et al., 2016 who evaluated the metabolic markers including BMI (BMI<27.0 kg/m2 and BMI ≥ 27.0 kg/m2) to predict incident diabetes mellitus in statin-treated patients (from the Treating to New Targets and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels Trials) [35]. This study showed that the incidence of T2DM were increased and these changes were accentuated with statin therapy. The lowest incidence of T2DM in statin-treated patients was reported in subjects with normal blood glucose and BMI <27 kg/m2. In addition, the highest incidence of NOD (22%) was reported in the prediabetics with BMI ≥ 27 kg/m2 (Kohli et al., 2016). These results were in agreement with early work in Benghazi area by Kadiki and Roaed in the year 1999, reported about 60% of total type 2 DM subjects were obese [17]. Collectively the findings of these studies indicated that obesity is considered as a major risk factor for the incidence of NOD.

The effects of Atorvastatin on the glycemic control of the study population

The influence of statin treatment on insulin secretion and insulin resistance is not fully illustrated. In a clinical trial, Koh et al., 2010, demonstrated a substantial risk of using statins in the incidence of diabetes mellitus [36]. This work showed that atorvastatin 10mg increased FPG by 25% compared to a 45% increase by atorvastatin 80mg, and HbA1c levels also elevated by 2% and 5%, respectively. The later evidence suggested that the risk of developing NOD risk was enhanced by consuming atorvastatin. This work was in agreement with the findings of the current study in which both measures of glycemic control (FBG and HBA1c) were significantly higher in the Atorvastatin group compared with that of the non-statin control group (P<0.001and P<0.001, respectively). Another work by Simsek et al., 2012, was in accordance with our findings, in which the high-dose of atorvastatin showed

a significant increase in glycemic control (indicated by 0.3 increase of HbA1) compared to baseline values but without changes in FPG values [37].

In the present work, 17 patients had NOD out of 100 patients on Atorvastatin treatment, whereas, no NOD cases were reported in the non-Atorvastatin group. In accordance, Lin et al. (2016) analyzed data of about 30,000 patients suffering from acute coronary syndromes to assess the influence of consuming statins against patients who were not on statins to determine the risk of NOD [38]. The author reported that the risk of NOD was increased in statin-consuming patients compared with the control (no statin use). Furthermore, the hazard ratios changed depending on the type of statin the patients consumed, and all of them were statistically significant except for lovastatin. The risk was highest in Rosuvastatin (hazard ratio was 1.42) followed by Fluvastatin and Atorvastatin (hazard ratios were 1.38 and 1.30, respectively). Another work was in agreement with our study, Preiss et al., 2011, reported on five large clinical trials that compared the influence of higher against lower doses of statins upon the prevalence of NOD and showed that each of them had an odds ratio point estimate greater than 1 for higher doses to increase NOD incidence [39].

In recent evidence, Sattar 2023 reported that randomized trials concluded that moderate-dosage statins elevate NOD risk by about 11% and high-dosage may elevate the risk by 20% or more compared with control (subjects consuming placebo) [40]. On the contrary, in a clinical trial in China, the atorvastatin-consuming subjects showed no significant glycemic control difference compared with the control, but this was a low-standard study that included 80 patients, and the actual dose of atorvastatin used was not mentioned [41].

Mechanism of statin diabetogenicity

It is well established that type 2 diabetes has been associated with two main metabolic abnormalities: the first is insulin insensitivity and diminished β-cell function. However, many other complications such as a change in the renal threshold for glycosuria, abnormal regulation of glucagon, and inflammation are also linked to type 2 diabetes (Hoogwerf, 2023). Statins and other Lipid-lowering drugs influence glycemic control and insulin sensitivity in various ways. The effects are manifested in glycosylated Hb and blood glucose. However, the exact underlying molecular mechanisms implicated in the development of NOD are not yet fully illustrated [42].

The effects of statin treatment on pancreatic β-cells lead to decreased activity of GLUT2 in the cell membrane which leads to decreased glucose uptake. These effects include a decrease in isoprenoids and ubiquinone (coenzyme Q10) which finally reduce ATP synthesis. Statins lead to reduced activity of the K+ channel and block the Ca^{+2} channels. Statin also led to an increase in LDL receptors (LDLR) which subsequently caused an increase in intracellular cholesterol that ultimately led to lipotoxicity and β-cell death. All these effects result in two things. Reduce beta cell insulin secretion). These effects collectively lead to reduced exocytosis of insulin granules and reduction in β-cell mass [43]. It is worth mentioning that these effects are more obvious in the case of using lipophilic statins like Atorvastatin than with hydrophilic statins such as pravastatin [44].

In peripheral tissue, statin use leads to various effects that ultimately cause insulin resistance and an increase in blood glucose levels. These influences include the downregulation of GLUT4 in adipocytes and a reduction in GLUT4 translocation across the cell membrane. The

decrease in insulin signaling leads to decreased adipocyte maturation and differentiation [45]. As clear from the studies on the mechanisms of statin-linked NOD, the most reliable explanation is the implication of statin in insulin resistance [46]. However, this has not been examined by conducting large studies on the effect of statin on the incidence of NOD. Furthermore, genetic studies reported the risk of having NOD due to weight gain. This effect was obvious from the Mendelian randomization data reported by Yang and Schooling (2023), who concluded that about half of the statin-associated risk of diabetes incidence comes from modest weight gain [47].

In 2023, Laakso and Silva discussed the impact of genetic variants on the function of statins and their correlation with the risk of developing new-onset Type 2 diabetes (T2D). The study showed that genetic variants in three specific genes may affect statin function, namely the solute carrier organic anion transporter family member 1B1 gene (SLCO1B1), 3-Hydroxy-3-Methylglutaryl-CoA Reductase (HMGCR), and Low-Density Lipoprotein Receptor (LDLR) [48].

There was no significant correlation found between SLCO1B1 and the risk of T2D, elevated glucose levels, insulin resistance, or impaired insulin secretion [49]. The HMG-CoA reductase enzyme (key enzyme for cholesterol synthesis) is inhibited by statins, which leads to a decrease in the synthesis of mevalonate and cholesterol. The importance of the HMG-CoA gene as a risk factor for Type 2 diabetes has been established through multiple studies. In their analyses, Swerdlow et al., (2015) analyzed 223,463 subjects from 43 genetic studies. The study found that the HMGCR rs17238484-G allele was linked to a 2% increase in risk for T2D. Further research is required to validate the initial findings since the modifications were minor [50].

Homozygous or heterozygous pathogenic mutations in the LDLR gene are responsible for familial hypercholesterolemia. Mutations of this kind cause the LDL receptors to be expressed or facilitate the transport of LDL-C into cells [51]. There is mounting evidence that suggests higher levels of LDL-C may decrease one's risk of developing T2D. However, there is currently no conclusive evidence to suggest that this correlation is causal in nature [52-54].

In agreement with our work, Abbasi and other researchers (2001), conducted a 10-week clinical trial on 71 individuals who did not have CVD or T2D at the start, administering atorvastatin 40 mg daily. The study showed that atorvastatin caused an 8% increase in insulin resistance and a 9% increase in insulin secretion compared to baseline measurements. During the trial, the elevation in insulin secretion was observed to compensate for the insulin resistance caused by atorvastatin. However, in another study that spanned over 6 years, the pancreas could not compensate for the increasing insulin resistance, leading to a reduction in insulin secretion [33]. It is clear from all of the studies on the genetic variants that there is no strong evidence to support the causal effect of statins on the prevalence of new-onset type 2 diabetes. Despite the possible risks of having diabetes as an impact of using statins, a recent review by Hoogwerf 2023 concluded that the benefits of statins in the protection against CVD episodes still outweigh the risks of NOD [42].

Study limitations

The current study did not investigate the mechanisms underlying the diabetogenic impact of statins. Due to technical and financial limitations, the study was unable to measure

the levels of insulin and the markers of insulin resistance to have a complete picture about the diabetogenic action of atorvastatin on the study population.

Conclusion and Recommendation

The present work demonstrated that atorvastatin treatment was significantly implicated in the development of NOD. The risk of developing NOD increases by increasing the intensity of statin and this risk also becomes greater when patients have more diabetes risk factors at baseline such as obesity and increasing age. The present study also showed that the statin using male gender showed a greater risk of developing NOD than the female gender. The present work recommends clinicians warn the patients of the slight risk of developing diabetes after using statins, especially atorvastatin. Patients also should be told to make changes in their lifestyle to decrease the diabetes risk and also to improve their CVD status and prognosis. Patients are also advised to measure their FBG and HbA1c regularly during the period of statin treatments and the doctors should tailor the lifestyle plan for the patients according to the lab results.

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