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Comparison of Lipid Profile, Liver Enzymes, Creatine Kinase and Lactate Dehydrogenase Among Type II Diabetes Mellitus Patients on Statin Therapy

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Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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Background: Diabetes mellitus (DM) is an epidemic disease affecting millions worldwide; the majority being type 2 diabetes mellitus (T2DM). Diabetes mellitus has been shown to be an important risk factor for the development of a variety of cardiovascular diseases, which are becoming common in Ethiopia. Consequently, risk-reducing statin therapy is recommended for nearly all patients with T2DM at 40 years of age or older regardless of cholesterol level. However, some controversies exist regarding its safety.

Objective: The aim of this study was to assess and compare the levels of lipid profile, liver enzymes, creatine kinase-MB (CK-MB) and lactate dehydrogenase (LDH) among T2DM patients on statin therapy.

Methodology: A hospital-based cross-sectional study was conducted on a total of 100 T2DM patients. The study participants were divided into four groups consisting of equal numbers of participants (n = 25). Group I, II, and III were T2DM patients who were on statin therapy for 14 days–6 months, 6–18 months and >18 months, respectively. Group IV consisted of T2DM patients who were not on statin therapy. Convenient sampling technique was implemented till the required number had been achieved. Sociodemographic data was collected by using a standardized questionnaire. Fasting blood was collected and lipid profile, liver enzymes, CK-MB, LDH and fasting blood sugar were analyzed. Data was entered using epi-data and analyzed by one way ANOVA followed by Tukey post hoc multiple comparison tests using SPSS V. 20.00. A *P*-value < 0.05 was considered statistically significant.

Results: The mean values of total cholesterol and TAG were significantly lower among group III as compared to group I (*P*-values = 0.019 & 0.01). Similarly, LDL-c was significantly lower among group III as compared to group I (*P* = 0.022) and group IV (*P* = 0.027). Serum liver enzymes, CK-MB and LDH were not significantly different among the study groups (*P* > 0.05). The mean values of alanine aminotransferase (ALT) and AST were found within normal range while mean ALP was higher in all study groups. Fasting blood glucose value was not significantly different among the study groups, but higher than normal cut-off value in all groups.

Conclusion: Statin therapy taken for a longer time has an effect in lowering total cholesterol, LDL-c and TAG in T2DM patients. Statin therapy has not brought significant change on CK-MB, LDH, liver enzymes and other parameters among T2DM patients.

Keywords: CK-MB, HMG-CoA reductase, lipid profile, liver enzymes, statin, T2DM, LDH

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Introduction

Diabetes is a serious chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. It is characterized by hyperglycemia with disturbances of carbohydrates,

fat and protein metabolism.¹ In Ethiopia, occurrences and complications of DM have been increasing over time at an alarming rate.² The starting point for living well with diabetes is an early diagnosis followed by glycemic control.³ One of the consequences of metabolic syndrome as a result of diabetes is dyslipidemia, which is characterized by elevated fasting and postprandial triglycerides (TG), low level of high density lipoprotein cholesterol (HDL-C), elevated level of low density lipoprotein-cholesterol (LDL-C) and the predominance of small dense LDL-C particles. Several studies have indicated that diabetic dyslipidemia is caused by impaired action of lipoprotein lipase (LPL) that is localized in the endothelial cells. Modified LDL such as glycated and oxidized LDL that play an important negative role to induce vascular and renal cellular dysfunction and cardiovascular risk which in turn hasten diabetic complications.^{4–6} Non-pharmacologic interventions (diet and exercise) are first line therapies and are adjuvant to the pharmacologic therapy when necessary in the treatment of diabetic dyslipidemia. Lowering LDL-C level is the first priority in treating diabetic dyslipidemia mainly circulating levels of smaller and denser LDL particles.

High plasma level of LDL-C contributes to plaque formation in the arteries that narrows blood vessels and restrict blood flows. Under such conditions, statins are the first drug of choice, followed by resins, ezetimibe, fenofibrate, niacin and others. If a single agent is inadequate to achieve lipid goals, combinations of the drugs may be used.^{7,8} Targets for LDL-C level are very important in choice of a pharmacological lipid-lowering agent. LDL-C < 1.8 mmol/L (70 mg/dL) and TG < 2.3 mmol/L (204 mg/dL) values are greatly desired for very high risk patients.⁹ Statin lowers atherogenic LDL-C through inhibition of 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase, the rate-limiting enzyme of cholesterol biosynthesis and upregulation of LDL receptors on the cell membrane. Statin reduces CVD by 25–30%.¹⁰ Statin has been introduced as the best cholesterol lowering drug since 1987 and it includes; atorvastatin, simvastatin, pravastatin and rosuvastatin.¹¹ In addition, statin has anti-inflammatory, immunomodulation and anti-microbial effects.^{12,13} As a result, statins are considered very effective in reducing cardiovascular morbidity and mortality in high-risk patients like those with T2DM.¹⁴

Even if the safety of statins was well established, several clinical studies have demonstrated evidence of liver toxicity and statin-associated myopathy. Studies indicated that genetic

and environmental factors determine statin-induced liver and muscle toxicity and its effectiveness as well.^{14–16} The other concern over statin safety is myopathy and rhabdomyolysis, which is characterized by increased activity of CK and LDH.^{16,17} There is no well documented study done to examine the extent of compliance and adherence to progression of liver function tests, serum CK and LDH level among T2DM patients receiving lipid-lowering drugs like statins in Ethiopia.

Higher doses of statins have been linked to an increased risk of a life-threatening form of muscle breakdown called rhabdomyolysis. This can lead to permanent kidney damage, coma, and death. Symptoms include fatigue, muscle pain, muscle tenderness, muscle weakness, nocturnal cramping and tendon pain. The mechanism of statin-induced myopathy could be impaired synthesis of cholesterol leading to changes in the cholesterol in myocyte membranes and behavior of the membrane, impaired synthesis of compounds in the cholesterol pathway (coenzyme Q10) and depletion of isoprenoids, which prevents myofibril apoptosis.^{18–20}

Measuring serum CK is an important part of the evaluation of patients with muscle weakness or myalgia, and assessing of patients with myopathies or muscle injuries.²¹ Similarly, evaluation of serum LDH or LDH isoenzyme is relevant in the diagnosis, prognosis and monitoring of diseases such as myocardial infarction, hemolytic anemia, hepatocellular carcinoma, ovarian dysgerminoma and testicular germ cell tumor.^{22,23}

Therefore, the present study was conducted to compare lipid profile, liver enzymes, creatine kinase and lactate dehydrogenase among type II diabetes mellitus patients on statin therapy at Tikur Anbessa Specialized Hospital (TASH) in Addis Ababa, Ethiopia.

Materials and Methods

Study Area and Period

This study was conducted at the Diabetic Clinic of Tikur Anbessa Specialized Hospital (TASH), Ethiopia from March, 2017 to September, 2017.

Study Design

A hospital-based cross-sectional study design was used to determine serum level of liver enzymes (alanine aminotransferase, ALT; AST and ALP), CK-MB isotype, LDH and lipid profiles (LDL, HDL, TAG and total cholesterol) among T2DM patients who were receiving statin and not receiving statin at the Diabetic Clinic of TASH

within the study period. Since the study aimed at assessing the effect of statin drugs on lipid profile, liver enzymes, creatine kinase-MB (CK-MB) and lactate dehydrogenase (LDH) among T2DM patients with respect to duration of therapy, the study participants were grouped into four groups. Group I, II, and III were T2DM patients who were on statins for 14 days–6 months, 6–18 months and >18 months respectively. Group IV consisted of T2DM patients who were not on statin therapy. The number of study participants in each group was 25. Blood analysis was conducted at Zewditu Memorial Hospital, Ethiopia and at the Ethiopian Public Health Institution clinical chemistry laboratory unit.

Inclusion and Exclusion Criteria

T2DM patients who were on statin drugs, and T2DM patients who were not on statin drugs as a control group were included in this study. Patients who had any clinical evidence of cirrhosis or other causes of chronic liver disease, diagnosed T1DM, pregnancy, lactating mother, children less than 18 years of age, patients using HIV drugs and patients with known muscular and cardiac disease were excluded from this study.

Data Collection

Body Mass Index (BMI) and Waist-to-Hip Ratio (WHR)

Body mass index is a useful clinical calculation to diagnose obesity because it is correlated with total body fat. Values of BMI can be classified as follows. BMI ≤ 18.5 Underweight, BMI =18.5–24 normal weight, BMI=25–29.9 overweight and BMI ≥ 30 obese. BMI has been calculated as weight (kg) divided by height in square meters (m^2). Waist-to-hip ratio to measure obesity which in turn is a possible indicator of other more serious health problems. According to WHO, WHR of above 0.9 for male and 0.8 for female is considered as abdominal obesity. Weight, height, waist and hip circumferences were measured by an experienced nurse and BMI and WHR were calculated.

Blood Sample Collection

A total of 5 mL of venous blood was drawn from each T2DM patient using a disposable plastic syringe. The blood was poured into a serum separator tube (SST) and then centrifuged after it was clotted. The serum was kept at -80°C in a refrigerator till biochemical analysis was carried out. Liver enzymes (AST, ALT, ALP), CK-MB, LDH and lipid profile (LDL, HDL, TAG and total cholesterol) were measured with

a spectrophotometer Cobas c analyzer. Manufacturer instructions of reagent and instrument were strictly followed.²⁴

Data Analysis

The questionnaires were checked for completeness. Collected quantitative data was coded, entered into a computer, processed, edited, and analyzed using EPI-INFO and SPSS (version 20). One-way analysis of variance (ANOVA) was done to determine statistical differences among all groups of the study participants. Pairwise comparisons were conducted by Tukey post hoc multiple comparison tests. *T*-test also used to compare data between groups. The results of the data were presented as mean \pm standard deviation (SD). A *P*-value < 0.05 was considered statistically significant.

Ethical Considerations

This study was conducted in accordance with the declaration of Helsinki Oct 2008 (DoH/Oct2008). The ethical clearance was obtained from the Department of Biochemistry Research and Ethical Review Committee (DRERC), by approval letter with Ref. No. of SOM/BCHM/151/2009, meeting No. of DRERC 01/17 and protocol No. of M.Sc. 8/17 issued on March 09/2017. A consent form (Figure 1), prepared with detailed explanation of objectives, risks and benefits of the study was presented to the participants and the confidentiality was strictly kept. Data was collected after obtaining informed consent and agreement from the patients under study. Sample collection was performed by trained health professionals following ethical steps and scientific procedures.

Results

Among the total participants, 48/100 (48%) were males and 52/100 (52%) were females and the numbers of male and female in each group were more or less similar. The mean age of the participants in groups I, II, III and IV was 57 ± 7.77 , 55.28 ± 7.51 , 58.4 ± 9.36 and 52.9 ± 8.46 years, respectively. The total (ground) mean age was 55.92 ± 8.69 years, ranging between 38 and 74 years. About 89/100 (89%) of the study participants had been educated up to preparatory and above and 11/100 (11%) were illiterate. None of the study participants were on the highest dose (80 mg) of statin therapy. About 40/75 (53.3%) and 35/75 (46.7%) of the study participants used 20 mg and 40 mg statin drugs respectively.

Of the total participants in this study, simvastatin, atorvastatin, lovastatin and fluvastatin were used by 29/

CONSENT FORM

In undersigning the objective of this study, entitled, “comparison of liver enzymes, creatine kinase and lactate dehydrogenase at different period of T2DM patients who are on statin attending diabetic clinic of Tikur Anbesa Specialized Hospital Addis Ababa, Ethiopia”, I am giving my consent to participate in the study. I have been informed that the purpose of this study is to assess serum level of liver enzymes, creatine kinase and lactate dehydrogenase and associated risk factors at different period of T2DM patients who are on statin attending diabetic clinic of Tikur Anbesa Specialized Hospital Addis Ababa, Ethiopia, I have understood that participation in this study is entirely voluntarily. I have been told that my answers to the questions will not be given to anyone else and no reports of this study ever identify me in any way. I have also been informed that my participation or non-participation or my refusal to answer questions will have no effect on me. I understood that participation in this study does not involve risks. I understood that Mezgebu legesse is the contact person if I have questions about the study or about my rights as a study participant.

Respondent's signature_____

Interviewer

Name _____ Signature _____ Date _____

Figure 1 Study consent form.

75 (38.67%), 28/75 (37.33%), 15/75 (20%) and 3/75 (4%) respectively as anti-dyslipidemia drugs (Figure 2).

This study indicated that metformin was the most frequently prescribed (44/100, 44%) anti-glycemic drug followed by insulin (19/100, 19%) among the study participants. And around 37/100 (37%) of the participants were on a combination of anti-glycemic drugs (Figure 3).

The mean SBP, DBP, BMI, and WHR were not significantly different among the four study groups. One way ANOVA indicated that mean SBP in T2DM patients who were on statin drugs for >18 months was higher (142 mmHg) as compared with other study groups. Groups of study participants who were on statins for 14 days 6 months and who were not on statin therapy had similar mean SBP. The mean DBP was found to be in normal range among all study groups. The mean values of

BMI and WHR were higher than normal reference ranges in all study groups (Table 1).

The mean values of LDL, TAG, and total cholesterol showed statistically significant differences among the four study groups as determined by one way ANOVA. Post hoc Tukey's test revealed that total cholesterol and TAG were significantly lower in group III than in group I ($P=0.019$ & 0.01), LDL was significantly lower in group III than in group I ($P=0.022$) and group IV ($P=0.027$). But, HDL-cholesterol and fasting blood glucose did not indicate a statistically significant difference among the study groups (Table 2).

In this study, the mean level of serum liver enzymes (ALT, AST and ALP) showed slight elevation among T2DM patients who were on statin therapy for greater than 18 months as compared to other study groups but,

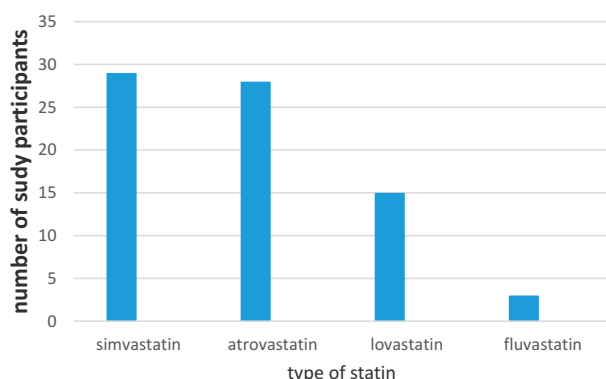


Figure 2 Frequency of statin type used by study participants.

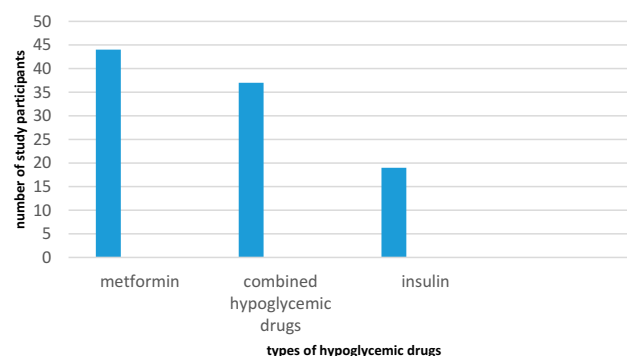


Figure 3 Type of hypoglycemic drugs used by study participants.

Table 1 Anthropometric and Clinical Characteristics of T2DM Patients Who Were on Statin Drugs

Variable	Groups	Mean \pm SD	P-value
SBP	14 days–6 months (n=25)	136.40 \pm 14.40	0.418
	6 months–18 months (n=25)	133.44 \pm 15.19	
	>18 months (n=25)	142.00 \pm 20.62	
	Not on statin therapy (n=25)	136.80 \pm 21.55	
	Total (N=100)	137.16 \pm 18.20	
DBP	14 days–6 months (n=25)	80.40 \pm 6.76	0.494
	6 months–18 months (n=25)	79.36 \pm 9.59	
	>18 months (n=25)	82.76 \pm 9.33	
	Not on statin therapy (n=25)	82.80 \pm 12.08	
	Total (N=100)	81.33 \pm 9.60	
BMI	14 days–6 months (n=25)	26.43 \pm 3.10	0.052
	6 months–18 months (n=25)	26.69 \pm 3.73	
	>18 months (n=25)	28.99 \pm 5.89	
	Not on statin therapy (n=25)	26.00 \pm 2.99	
	Total (N=100)	27.03 \pm 4.20	
WHR	14 days–6 months (n=25)	0.96 \pm 0.10	0.754
	6 months–18 months (n=25)	0.95 \pm 0.06	
	>18 months (n=25)	0.97 \pm 0.10	
	Not on statin therapy (n=25)	0.97 \pm 0.06	
	Total (N=100)	0.96 \pm 0.07	

Abbreviations: SBP, Systolic blood pressure; DBP, Diastolic blood pressure; BMI, Body mass index; WHR, Waist-hip-ratio.

statistically not significant. The mean values of both serum ALT and AST in all study groups were found within normal reference ranges (Tables 3 and 4).

One way ANOVA showed serum level of CK-MB isotype was higher among T2DM patients who were on statin therapy for greater than 18 months as compared to other study groups, but not statistically significant. For all study groups, serum mean value of CK-MB isotype was found within the normal reference range (CK-MB < 25 U/L). The mean value of LDH was higher among T2DM patients who were on statin for 14 days/6 months and greater than 18 months, but statistically not significant. For all study groups mean values of LDH were found within the normal reference range (Table 4), but it was pulled to the upper limit (Table 5).

There was an elevation of serum total cholesterol and LDL among T2DM patients who were not on statin therapy as compared to T2DM patients who were on statin therapy. The mean values of liver enzymes (ALT, AST, and ALP), CK-MB isotype and LDH were slightly higher among T2DM patients who were on statin therapy than T2DM patients who were not on statin therapy but, statistically not significant. HDL-cholesterol was

Table 2 Serum Lipid Profile and Glucose Levels in T2DM Patients Who Were on Statin Therapy

Variables	Groups	Mean \pm SD (mg/dL)	P-value
TC	14 days–6 months (n=25)	216.04 \pm 59.36 ^a	0.022
	6 months–18 months (n=25)	186.16 \pm 50.89	
	>18 months (n=25)	172.48 \pm 46.57 ^b	
	Not on statin therapy (n=25)	202.56 \pm 49.55	
	Total (N=100)	194.31 \pm 53.62	
HDL-C	14 days–6 months (n=25)	34.60 \pm 9.60	0.820
	6 months–18 months (n=25)	32.56 \pm 10.36	
	>18 months (n=25)	35.28 \pm 13.749	
	Not on statin therapy (n=25)	34.64 \pm 8.12	
	Total (n=100)	34.27 \pm 10.547	
LDL-C	14 days–6 months (n=25)	139.88 \pm 41.75 ^a	0.008
	6 months–18 months (n=25)	118.48 \pm 38.90	
	>18 months (n=25)	107.60 \pm 35.364 ^c	
	Not on statin therapy (n=25)	139.16 \pm 40.21 ^d	
	Total (N=100)	126.28 \pm 40.94	
TAG	14 days–6 months (n=25)	233.84 \pm 108.146 ^a	0.018
	6 months–18 months (n=25)	191.64 \pm 89.75	
	>18 months (n=25)	148.24 \pm 69.87 ^b	
	Not on statin therapy (n=25)	177.56 \pm 107.29	
	Total (N=100)	187.82 \pm 98.61	
FBG	14 days–6 months (n=25)	167.24 \pm 53.44	0.662
	6 months–18 months (n=25)	164.80 \pm 48.87	
	>18 months (n=25)	169.60 \pm 76.79	
	Not on statin therapy (n=25)	185.60 \pm 73.98	
	Total (N=100)	171.81 \pm 63.99	

Notes: ^aIndicates significant differences compared to group III; ^bIndicates significant differences compared to group I; ^cIndicates significant differences compared to group I&IV; ^dIndicates significant differences compared to group III at P < 0.05 as tested by Tukey post hoc multiple comparisons.

Abbreviations: TAG, Triacylglycerol; LDL, Low density lipoprotein; HDL, High density lipoprotein; TC, Total cholesterol; FBG, Fasting Blood glucose.

more or less similar among T2DM patients who were on statin and those had not yet started on statin drugs (Table 6).

The mean values of total cholesterol, LDL and TAG were higher among T2DM patients who were on 20 mg statin therapy as compared to T2DM patients who were on 40 mg statin therapy but, statistically not significant. The mean values of liver enzymes (ALT, AST, and ALP), CK-BM

Table 3 Comparison of Liver Enzymes (ALT, AST and ALP) in T2DM Patients Who Were on Statin Therapy

Variable	Groups	Mean \pm SD (IU/L)	P-value
ALT	14 days–6 months (n=25)	23.08 \pm 14.1	0.452
	6 months–18 months (n=25)	19.88 \pm 6.8	
	>18 months (n=25)	23.92 \pm 8.9	
	Not on statin therapy (n=25)	21.2 \pm 10.4	
	Total (N=100)	22.2 \pm 10.3	
AST	14 days–6 months (n=25)	20.2 \pm 7.9	0.638
	6 months–18 months (n=25)	19.6 \pm 4.9	
	> 18 months (n=25)	22.6 \pm 6.9	
	Not start statin (n=25)	19.4 \pm 10.7	
	Total (N=100)	20.3 \pm 7.9	
ALP	14 days–6 months (n=25)	195.7 \pm 45.4	0.189
	6 months–18 months (n=25)	187.2 \pm 57.2	
	> 18 months (n= 25)	215.7 \pm 74.3	
	Not start statin (n=25)	184.6 \pm 36	
	Total (N=100)	195.6 \pm 55.7	

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase; n, Numbers participants in each groups; N, Total study subjects.

Table 4 Reference Cut- off- Value for Biochemical Parameters Performed in the study. Reference Range for Lipid Profiles

Parameters	Desirable	Borderline	High
TC	<200 mg/dL	200–239 mg/DL	>240 mg/dL
TG	<150 mg/dL	150–199 mg/dL	>200 mg/dL
LDL-C	<129 mg/dL		>160 mg/DL
HDL-C	\geq 60 mg/dL		

Table 5 Comparison of LDH and CK-MB Isotype Among T2DM Patients Who Were on Statin Drugs

Variable	Groups	Mean \pm SD (IU/L)	P-value
LDH	14 days–6 months (n=25)	191.6 \pm 77.9	0.270
	6 months–18 months (n=25)	174.3 \pm 38.7	
	>18 months (n=25)	191.7 \pm 32.3	
	Not start statin (n=25)	168.8 \pm 44.1	
	Total (N= 100)	181.6 \pm 55.7	
CK-MB	14 days–6 months (n=25)	13.6 \pm 13.0	0.652
	6 months–18 months (n=25)	15.3 \pm 5.3	
	>18 months (n=25)	17.01 \pm 8.0	
	Not start statin (n=25)	14.7 \pm 10	
	Total (N=100)	15.2 \pm 9.7	

Abbreviations: LDH, Lactate dehydrogenase; CK-MB isotype, Creatine kinase of heart muscle isotype; n, Numbers of study participants in the study groups; N, Total numbers of study participants.

isotype and LDH were slightly lower among T2DM patients who were on 20 mg statin therapy than T2DM patients who were on 40 mg statin therapy but statistically they were not significant (Table 7).

Table 6 Comparison of Biochemical Parameters Among T2DM Who Were on Statin and T2DM Who Were Not on Statin Therapy

Parameter (Mean \pm SD)	T2DM Who Were on Statin (n=75)	T2DM Who Were Not on Statin (n=25)	P-value
TC (mg/dL)	192 \pm 54.9	203 \pm 49.5	0.377
LDL-C (mg/dL)	122 \pm 40.5	139 \pm 40.2	0.069
HDL-C (mg/dL)	34.15 \pm 11.3	34.64 \pm 8.2	0.841
TAG (mg/dL)	177 \pm 96	191 \pm 107	0.551
FBG (mg/dL)	167 \pm 60	185 \pm 73.9	0.215
ALT (IU/L)	22.49 \pm 10.4	21.2 \pm 10.6	0.593
AST (IU/L)	20.6 \pm 6.7	19.5 \pm 10.7	0.540
ALP (IU/L)	199.4 \pm 60.5	184.2 \pm 36.4	0.237
CK-MB (IU/L)	15.3 \pm 9.4	13.7 \pm 10.9	0.587
LDH (IU/L)	185.88 \pm 53.5	168.7 \pm 44.1	0.152

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BD, Blood glucose; CK-MB, Creatine kinase heart isotype; HDL-C, High density cholesterol; LDH, Lactate dehydrogenase; LDL-C, Low density lipoprotein cholesterol; SD, Standard deviation; TAG, Triacylglycerol; TC, Total cholesterol.

Table 7 Comparison of Biochemical Parameters Among T2DM Patients Who Were on 20 mg Statin Therapy and T2DM Patients Who Were on 40 mg Statin Therapy

Parameter (Mean \pm SD)	T2DM Who Were on 20 mg Statin (n=40)	T2DM Who Were on 40 mg Statin (n=35)	P-value
TC (mg/dL)	203.6 \pm 57	181 \pm 51	0.076
LDL-C (mg/dL)	131 \pm 41	114 \pm 38	0.071
HDL-C (mg/dL)	33.4 \pm 11.6	35 \pm 11	0.530
TAG (mg/dL)	209.6 \pm 112	175 \pm 76	0.122
FBG (mg/dL)	174 \pm 46	160.5 \pm 70	0.308
ALT (IU/L)	20.68 \pm 11.0	24.57 \pm 9.4	0.107
AST (IU/L)	20.0 \pm 7.3	20.94 \pm 5.9	0.682
ALP (IU/L)	196.7 \pm 37.5	202.2 \pm 75.5	0.670
CK-MB (IU/L)	14.4 \pm 6.3	15.7 \pm 11.4	0.654
LDH (IU/L)	175.2 \pm 34	195.2 \pm 64	0.106

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BD, Blood glucose; CK-MB, Creatine kinase heart isotype; HDL-C, High density cholesterol; LDH, Lactate dehydrogenase; LDL-C, Low density lipoprotein cholesterol; SD, Standard deviation; TAG, Triacylglycerol; TC, total cholesterol.

One way ANOVA showed that the mean values of serum total cholesterol and LDL cholesterol had statistically significant differences among T2DM patients who were on metformin + statin, T2DM patients who were on insulin + statin therapy and T2DM patients who were on combined hypoglycemic drugs + statin (P-value=0.034 for total cholesterol and 0.046 for LDL-cholesterol). A Tukey Post hoc test showed that the mean values of serum total cholesterol and LDL cholesterol were significantly higher

Table 8 Comparison of Lipid Profile, Blood Glucose, Liver Enzymes, CK-MB and LDH Among T2DM Patients Who Were on Metformin + Statin, Insulin + Statin and Combined Hypoglycemic Drugs + Statin Therapy

Parameter (Mean±SD)	Treatment			P-value
	Metformin + Statin (n=34)	Insulin + Statin (n=17)	Combined Hypo- glycemic + Statin (n=24)	
TC (mg/dL)	209.±54.5	171.6±50	191±54.9	0.034*
LDL-C (mg/dL)	138±40	110±36	112±39.9	0.046*
HDL-C (mg/ dL)	29.9±12.8	36±10.8	33.2±10	0.092
TAG (mg/dL)	205.9±100	153.2±51	197.4±109	0.169
FBG (mg/dL)	174±63.4	147±67	170.6±52	0.936
ALT (IU/L)	22.18±10	19.94±8	24.75±12	0.342
AST (IU/L)	21.5±7.3	18.71±4.3	20.3±7.1	0.372
ALP (IU/L)	208.3±67	203.2±75	184.2±31	0.317
CK-MB (IU/L)	16.7±12	14.2±7.3	14.3±5.9	0.508
LDH (IU/L)	193±69.4	190.88±34.2	171±33.6	0.254

Note: *Statistically significant difference.

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BD, Blood glucose; CK-MB, Creatine kinase heart isotype; HDL-C, High density cholesterol; LDH, Lactate dehydrogenase; LDL-C, Low density lipoprotein cholesterol; SD, Standard deviation; TAG, Triacylglycerol; TC, Total cholesterol.

among T2DM patients who were on metformin + statin therapy than T2DM patients who were on insulin + statin therapy. The mean value of HDL cholesterol was higher in T2DM patients who were on insulin + statin therapy than in the other two groups. The mean values of serum glucose, liver enzymes (ALT, AST, and ALP), CK-MB isotype and LDH were not significantly different among the three groups (Table 8).

Discussion

Dyslipidemia is one of the most characterized metabolic syndromes as a result of diabetes, especially T2DM patients who are considered a high risk group for developing CVD.^{4,5} As a result, all T2DM patients above the age of 40 years are recommended to take anti-dyslipidemic drugs, mainly statins.²⁵ Statins, HMG-CoA reductase inhibitors, are the most widely used medications for decreasing LDL cholesterol and play a vital role in the prevention of atherosclerotic cardiovascular complications.¹⁹ In the present study, simvastatin, atorvastatin and lovastatin were prescribed for 29 (38.7%), 28 (37.3%) and 15 (20%) of the total 75 study participants, respectively.

Statin works by inhibiting HMG-CoA reductase, causing upregulation of the LDL-C receptors on the surface of the liver cell and increasing the removal of LDL-C from the blood. HMG-CoA reductase is a rate-limiting enzyme in cholesterol biosynthesis. In addition, statins lower serum triglycerides concentrate and modify endothelial function, inflammatory responses, plaque stability, and thrombus formation. As a result, statin appears to play a major role in decreasing the risk of coronary heart disease (CHD) and all-cause mortality.^{26,27}

The results of the present study indicated that the mean serum values of total cholesterol, LDL- cholesterol, and TAG were significantly different among the four study groups (group I, II, III and IV). Post hoc Tukey's multiple comparison test revealed that total cholesterol and TAG concentration were significantly lowered in group III as compared to group I ($P=0.019$, 0.01). In addition, LDL cholesterol was significantly lowered in group III compared to group I ($P=0.022$) and group IV ($P=0.027$) (Table 2). Similarly, mean serum level of LDL-cholesterol was lower in T2DM patients who were on statin therapy than in T2DM patients who were not on statin therapy ($P=0.069$) (Table 6). The result of this study was in line with studies done by Trentman et al²⁶ and Stancu and Sima²⁸ to assess the efficacy of statin drugs. Other studies done to investigate the long term efficacy and safety of statin therapy by Takata et al,²⁹ Ford et al,³⁰ and Lu et al³¹ support this result.

The mean value of all serum lipid panels in all study groups were higher than the normal reference range, which may be due to T2DM. This is supported by a study done by Borle et al to assess dyslipidemia in T2DM patients which showed 86% had dyslipidemia.¹ Independent *t*-test in this study indicated that mean values of serum total cholesterol, LDL cholesterol, and TAG were higher among T2DM patients who were on 20 mg statin as compared to T2DM patients who were on 40 mg statin therapy (P -values= 0.076 for total cholesterol, 0.071 for LDL cholesterol, and 0.122 for TAG) (Table 7). This result agrees with a study done by Pedro-Botet et al¹⁹ that indicated high dose statin is necessary to achieve the desired plasma lipid goal. The mean values of serum total cholesterol and LDL cholesterol in this study were significantly different among T2DM patients who were on metformin + statin, insulin + statin and combined hypoglycemic drugs + statin therapy ($P = 0.034$ for total cholesterol and $P=0.046$ for LDL) (Table 8). These may be due to better glucose control potential and the multiple

effect of insulin in the metabolism of glucose and fat by muscle and other tissue.

The anatomic and physiologic nature of liver makes it central to metabolism of virtually every foreign substance including most drugs like statin.^{32–34} Results of the present study showed that the mean values of serum liver enzymes (ALT, AST, and ALP) had not shown statistically significant elevation among T2DM patients who were on statins for longer than 18 months as compared to the other groups. Both mean serum ALT and AST were found to be within the normal reference range (Table 9) in all of the study groups (Table 3). However, some studies revealed increased levels of aminotransferases in patients who were on atorvastatin therapy for 8 months.³⁵ Clinical trials done by Thapar et al³⁶ have shown that statin therapy has been associated with elevations in serum ALT levels in approximately 3% of persons who have received statin drugs. A study done in China by Gao et al³⁷ also indicated that ALT >1 × ULN was higher among statin users.

In the present study, absence of significant elevation in liver enzyme (ALT, AST and ALP) levels among statin users at different time periods may be due to the tolerability of statins by the study participants. Another reason may be due to the absence of high dose statin usage by the study participants (53.3% and 46.7% of the study participant used 20 mg and 40 mg statin, respectively). In addition, none of the participants in this study was a chronic alcoholic, a cigarette smoker or took drugs other than hypoglycemic and statin drugs. All the above factors have an impact on liver function and exacerbate adverse effects of statins. The mean serum value of ALP was above the normal reference range () in all the study groups (Table 2). Elevation of mean serum ALP in all of the study groups may be due to dyslipidemia as all groups of study participants had higher mean lipid profile and poor blood glucose control (Tables 2 and 3). Liver enzymes

(ALT, AST and ALP) showed statistically non-significant elevation among T2DM patients who were on statin therapy as compared to T2DM patients who were not on statin therapy (Table 6). These elevations of liver enzymes could be due to statins targetting liver for its antidyslipidemic effect and metabolism and its interaction with hypoglycemic drugs; thereby inducing mild hepatotoxicity.^{28,38,39}

Similarly, serum mean values of liver enzymes (ALT, AST and ALP) were higher among T2DM patients who were on 40 mg statin therapy than T2DM patients who were on 20 mg statin therapy (Table 7). These may be due to dose-dependent idiosyncratic drug-induced liver injury and its pathogenesis is complex and depends on different factors.⁴⁰ The mean values of liver enzymes (ALT, AST and ALP) among T2DM patients who were on metformin + statin, insulin + statin and combined hypoglycemic drugs + statin were not significantly different (Table 8). This may be due to the smaller sample size, study design effect, and degree of tolerability of hypoglycemic drugs and statin and their interaction by the liver.

Statin can induce muscle cell injuries by impaired synthesis of coenzyme Q10 (ubiquinone) for mitochondrial function, depletion of isoprenoids and disruption of cell membrane integrity.¹⁸ Quantitative measurement of serum Creatine kinase-MB (CK-MB) isotype has been reported to be useful for the diagnosis of myocardial infarction, re-infarction, and the size of infarction. Creatine kinase-MB can also be used as a secondary marker to aid in the diagnosis and measurement of the degree of myocardial necrosis as a result of drug toxicity.⁴¹ Out of the total CK isotypes found in the serum, CK-MB accounts for 6–25%. The finding of this study indicated that the mean serum level of CK-MB isotype was within normal reference range (Table 5) among T2DM patients who were on statin for greater than 18 months as compared to other study groups. This result is supported by a study done by Parker et al⁴² to measure serum CK before and after atorvastatin or placebo was administered for 6 months to 420 healthy, statin-naive subjects and indicated no individual CK value ≥10× ULN. Another study done by Soko et al⁴³ in Zimbabwe did not show any elevation of serum CK. A study done by Calza et al⁴⁴ showed that statin-induced elevation of CK is positively related with duration of statin use. A non-significant increase in CK-MB in our study may be due to the absence of high statin dose (80 mg), chronic alcoholism, cigarette smoking and drugs other than hypoglycemic and statin by the study participants.

The mean value of serum CK-MB isotype level among T2DM patients who were on statin therapy showed non-significant elevation as compared to T2DM patients who

Table 9 Reference Cut-off-Value for Biochemical Parameters Performed in the study. Reference Ranges for Liver and Heart Muscle Enzymes

Parameters	Normal Value	Higher
ALT	5–40 IU/L	>40 IU/L
AST	5–40 IU/L	>40 IU/L
ALP	35–130 IU/L	>130 IU/L
CK-MB	5–25 IU/L	>25 IU/L
LDH	140–280 IU/L	>280 IU/L

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CK-MB, Creatine kinase heart isotype; LDH, Lactate dehydrogenase.

were not on statin therapy (Table 6). The cause for serum CK elevation could be quite diverse, including excessive muscular stress and ischemia, genetic defects, and direct toxicity or physical damage, drugs and alcohol.⁴⁵ Statin drugs can disrupt the normal cardiac myocyte membrane integrity leading to release of intracellular components including structural proteins and enzymes such as CK-MB isotype in serum.⁴¹ Similarly, CK-MB isotype among T2DM patients who were on 40 mg statin was higher as compared to T2DM patients who were on 20 mg statin therapy (Table 7). A study done by Auer et al⁴⁶ showed as the doses of statins administered for patients increase muscle-related side effects will become more prevalent. Serum mean values of CK-MB isotype among T2DM who were on metformin + statin, insulin + statin and combined hypoglycemic drugs were not significantly different (Table 8).

Lactate dehydrogenase (LDH) is a cytoplasmic enzyme present in essentially all major organ systems. Ingestion of certain drugs, toxin and chemical poisons are among the major factors for LDH release to extracellular space.⁴⁷ Elevated serum LDH could act as a biomarker for diagnosis of drug-induced hepatic and muscular injury. Previously published works done by Tokinaga et al²⁰ and Noor et al⁴⁸ showed that statin therapy is responsible for moderate-to-severe elevation of serum LDH²⁰. The result of our study revealed that the mean serum level of LDH among T2DM patients who were on statin therapy for 14 days, 6 months and >18 months showed non-significant elevation as compared to T2DM patients who were on statin for 618 months and not on statin therapy (Table 3). Previously published works done by Tokinaga et al²⁰ and Noor et al⁴⁸ reported that statin drugs can increase serum LDH through disruption of cellular integrity, especially when it has been taken together with other drugs. As independent *t*-test showed, there was moderate elevation of mean serum LDH level among T2DM patients who were on statin therapy compared to T2DM patients who were not on statin therapy (Table 6). In addition, mean serum values of LDH among T2DM patients who were on 40 mg statin therapy were higher than LDH among T2DM patients who were on 20 mg statin therapy (Table 8). This result was supported by a case report done by Dragos et al³⁵ that showed elevation of LDH in T2DM patients who were on statin therapy.³⁵ Another case report described by Unnikrishnan and Satish⁴⁹ indicated that taking atorvastatin for several years elevated serum CK and LDH.

Conclusion

Statin drugs were found to have the effect of lowering lipid profiles (total cholesterol, LDL- cholesterol and TAG) in T2DM patients and the effects were found to be prominent in T2DM patients who were on statin drugs for more than 18 months. In addition, 40 mg statin dose produced a better effect on lipid profile as compared to 20 mg statin dose. In this study, insulin + statin showed better results in decreasing lipid profile levels. Moderate elevation of liver enzymes, CK-MB and LDH were observed among T2DM patients who were on statin therapy as compared to T2DM patients who were not on statin therapy. The mean values of ALT and AST were found within normal reference range in all study groups. ALP was higher than normal values among all study groups. According to this study statin did not show significant toxicity to liver and muscle.

Data Sharing Statement

All necessary data and materials related to the article are included in the manuscript.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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