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Effect of lipid lowering agents on lipid profile, blood glucose and Glycated hemoglobin in DM patients

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ABSTRACT:

Background: Lipid lowering agents are the cornerstone of primary and secondary prevention of cardiovascular disease. As diabetes is an important risk factor for cardiovascular disease and most patients with diabetes would benefit from statin therapy. The aim of the present study was to study the effect of lipid lowering agent on blood glucose, HbA1C and lipid profile among diabetic patients.

Methodology: A case control study was conducted in diabetic center at Benghazi city consists of 164 participants with diabetic dyslipidemia, 60 dyslipidemic non-diabetic and 37 healthy control were age and sex matching recruited from diabetic center, cardiac center and volunteers. Data collected was done by using self-constructed questionnaire and analyzed by using mean ± SD and T test was used for statistical differences at $\alpha < 0.05$.

Result: The data collected on 261shown that lipid lowering agent particularly simvastatin has significant effect on lowering FBG, PPBS and HbA1c. The dose of simvastatin has been found have effective role was 20 mg/day. Atorvastatin worked on another side in lowering serum, TG, cholesterol, HDL and VLDL and elevated HDL. Simvastatin was much better working in reduced FBS, PPBS and HbA1C in both types of diabetes while atorvastatin found better outcome for lowering lipid profile and elevated HDL in the type one diabetes mellitus and no differences in the previous parameters have been found among T2DM In compared to T1DM, lipid lowering agents simvastatin have shown great efficiency in reducing FBS, PPBS and HbA1C in T2DM.

Conclusion: Lipid lowering agents particular simvastatin improved glucose hemostasis and HbA1C while atorvastatin worked significantly in lowering lipid profile and elevated HDL. This data suggested that single dose of statin be given in diabetic patients without dyslipidemia as guideline treatment to reduced risk of diabetic induced CVD.

Key words: lipid lowering, Diabetes, FBS, PPBS, HbA1C, healthy control.

I. INTRODUCTION

Lipid lowering agents is the cornerstone of primary and secondary prevention of cardiovascular disease [1]. As diabetes is an important risk factor for cardiovascular disease and is considered a cardiovascular disease risk equivalent and treatment guidelines indicate that most patients with diabetes would benefit from statin therapy[2]. Atherogenic dyslipidemia is the most important modifiable risk factor implicated cardiovascular diseases development (CVDs) [3] and is frequently present in patients suffering from type II diabetes mellitus (T2DM).

Lipid lowering agents are still receiving a lot of challenges in the treatment of diabetic patients. There are two trials that reported conflicting results regarding new-onset diabetes with statins: An Intervention West of Scotland Coronary Prevention Study (WOSCOPS) and Trial Evaluating Rosuvastatin (JUPITER). JUPITER, a double-blind randomized study that used Rosuvastatin 20 mg or a placebo, reported that significant increase in median hemoglobin A1c levels in the rosuvastatin compared to the control group [4]. The WOSCOPS reported that diabetes was 30% lower inpatients taking pravastatin 40mg/day than with those taking a placebo [5]. One of the proposed mechanisms of influence of statins on glucose metabolism and insulin sensitivity include statins carry an anti-inflammatory effect that improves insulin sensitivity since inflammatory markers and proinflammatory cytokines are linked with insulin resistance[6].

Simvastatin has been reported to increase plasma glucose levels and reduce insulin

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sensitivity. A few studies have measured the effect of simvastatin treatment on glucose homeostasis. In a study by Koh et al. reported that simvastatin reduced insulin sensitivity[7]. Patients received simvastatin 80 mg/day had found that a 7% increase in mean plasma glucose levels after 2 months of treatment. Furthermore, patients on simvastatin 10, 20, 40, or 80 mg/day had increased insulin secretions this might be an indicative of deterioration in insulin sensitivity. Another study by the same authors showed significant reductions in insulin sensitivity after taking simvastatin 20 mg/day for 2 months. Nevertheless, there were no significant differences in insulin or glucose levels compared to baseline [8]. On the other hands,study by Bellia and his colleagues in which patients were selected randomly to receive either rosuvastatin 20 mg/day or simvastatin 20 mg/day showed that there was no effect of simvastatin on insulin sensitivity and glycemic control after 4 weeks of treatment [8]. In contrary, some studies have reported a lack of association between lipid lowering agents and blood glucose levels[9].

As lipid lowering agents used as cornerstones in treatment of diabetic dyslipidemia. There is a study showed that 55.9% of statin-treated patients in Lebanon and Jordan did not achieve goal levels for low-density lipoprotein cholesterol that were dependent on Systematic Coronary Risk Evaluation (SCORE) risk [10]. However, Statin therapy is the mainstay of treatment for treatment diabetic dyslipidemia [11].

So far, and according to our knowledge effect of lipid lowering agents on regulation lipid profile, glucose hemostasis and glycemic control in diabetic patients specially T1DM not get enough attention by authors.To date, the association between statins and lipid profile in diabetes has not been evaluated in the Libyan population. Therefore, statin might may use as regimen treatment in diabetic patients to reduced CVD incidence. This study aims at assessing the effect of different lipid lowering agents and doses on mean fasting blood glucose levels and glycosylated hemoglobin and lipid profiles in diabetic patients.

II. MATERIAL AND METHODS

Study population

A case control study carried out from beginning of December2019 to the end of April2020 on diabetes and non-diabetes subjects. Diabetes subjects include T1DM and T2DM from diabetes center. Non-diabetes volunteer matching to diabetes patients were selected from general population and/ or form diabetes center. Dyslipidemic non-diabetic were recruited from cardiac center. The total samples size were 261 subjects include healthy, dyslipidemic non diabetes and diabetes dyslipidemic (127 Male and 134 Female) diabetes dyslipidemic, dyslipidemic and healthy control with ages ranging between 15-70 years old.

The case and control were categorized as following

The patients in this study were diabetes dyslipidemic, dyslipidemic non-diabetes and healthy control and the sample was categorized as following:

- 164 patients with DM (70 T1DM and 94 T2DM) and have dyslipidemia.
- 60 patients with dyslipidemia non-diabetic.
- 37 Healthy control.

All patients (diabetic dyslipidemic and dyslipidemic patients) on lipid lowering agents prescribed by physicians were selected and followed up.

Blood biochemistry measurement

Measurement of FBS, PPBS, HbA1C and lipid profile have been done at the beginning and end of study.

Questionnaire.

The questionnaire for this study based on 20 items divided into four sections. It contained questions about personal information, Types of diabetes biochemical blood investigation types of lipid lowering agents.

Ethical statement

This study was approval by the local Ethics Committee of the Libyan international medical university (LIMU). Informed written consent was obtained through a consent form that was given to the participants along with the questionnaire.

Statistical analysis

The data from the questionnaires was entered using Excel. Data set was exported to SPSS v.22 and Epi-info for complete analysis. Statistical analysis was carried out for the complete sample which were created according to measurements in which frequencies and percentages were used. To determine the differences regarding each categorical variable in the groups, T test was performed. $p \leq 0.05$ was considered to be statistically significant.

III. RESULT:

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The data collected on 261 subjects shown that, 127 (48.7%) male and 134 (51.3%) female (Table 1). The average age of the subjects was 36 ± 4yearold, the most age of the subject in the study was those between 41-60 (57.1%) years old followed by age groups older than 60 years (23.4%) and the age groups between 15-18 years old being the least (1.1%) (Table 2).

The subject in this study was categorized as presented in table 3, age and gender matching in which total subjects with diabetic dyslipidemia 164, by which 81 (49.4%) and 83 (50.6%) male and female respectively. Dyslipidemicnon diabetic patients present by total subject 60 in which 28 (46.7%), 32 (53.3%) male and female respectively. In regarding total control subjects shown 37 among which 18 (48.6%) male and 19 (51.4%) female (Table 3).

Table 1: Gender distribution:

Gender	N	N %
Male	127	48.7%
Female	134	51.3%
Total	261	100.0%

Table 2: Age distribution:

Age in years	N	N %
15-18	3	1.1%
19-25	12	4.6%
26-40	36	13.8%
41-60	149	57.1%
More than 60	61	23.4%
Total	261	100.0%

Table 3: Distribution of gender among patients and healthy control:

	Diabetic and dyslipidemia patients							
	Diabetes dyslipidemia		Dyslipidemia non diabetic		Healthy control		Total	
	N	N %	N	N %	N	N %	N	N %
Male	81	49.4%	28	46.7%	18	48.6%	127	48.7%
Female	83	50.6%	32	53.3%	19	51.4%	134	51.3%
Total	164	100.0%	60	100.0%	37	100.0%	261	100.0%

In general effect of lipid lowering agents in both diabetic and non-diabetic dyslipidemia groups presented in table 4. In compared to control, simvastatin has great effect on lowering blood glucose, PPBS and HbA1C (P< 0.05) than the others lipid lowering agents. While atorvastatin has great significant effect on lowering lipid profile and elevated HDL levels than the other agents (P< 0.05) (Table 4).

Table 4:Effect of lipid lowering agents on targeted serum levels of both diabetes and non-diabetic dyslipidemic:

	Lipid lowering agents (all patients)				
	No (Control groups)	Simvastatin	Atorvastatin	Clofibrate	Rusovastatin
	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD
FBS	93±8	137±20	142±21	156±30	150±20
PPBS	113±12	157±21	295±34	189 ±24	190.±23
HBA1C	5.27±1	7.85±1	7.93±1	8.38±2	10.90±2
LDL	83.9±7	138.4±20	126.9±12	207.0±25	145.8±22
HDL	49.2±10	48.9±5	52.6±7	45.0±15	54.0±8

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VLDL	26.2±8	29.5±2	26.5±5	35.0±12	55.0±9
S. TG	131±23	148±31	132±15	175±25	275±35
S. Cho	145±34	202±40	192±24	179±23	216±26

T test has been used to compared between control and groups on lipid lowering agents at $\alpha < 0.05$).

Simvastatin was much better working in reduced FBS, PPBS and HbA1C in both types of diabetes while atorvastatin found have better than simvastatin outcome for lowering lipid profile and elevated HDL in type one diabetes mellitus and no differences found in T2DM by which both have almost similar effect. In compared to T1DM, lipid lowering agents simvastatin have shown great efficiency in reducing FBS, PPBS and HbA1C in T2DM (Table 5).

Table 5: Lipid lowering agents, diabetic dyslipidemia and Serum parameters:

	Types of diabetes mellitus									
	T1DM					T2DM				
	Types of lipid lowering agents					Types of lipid lowering agent				
	Health Control	Sim	Ator	Clof	Rusov	Healthy Control	Sim	Ator	Clof	Rusov
	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD
FBS	93±8	143±23	150±33	-	-	93±8	134±31	135±	156±34	150±13
PPBS	113±12	187±21	260±45	-	-	113±12	126±23	330±	188±44	210±22
HBA1C	5.27±1	7.81±1	8.49±2	-	-	5.27±1	7.36±2	7.55±	8.38±2	10.90±2
LDL	83.9±7	147±14	128±21	-	-	83.9±7	130± 23	126±	207±21	145.8±31
HDL	49.2±10	51.9±5	53.8±5	-	-	49.2±10	46.9±6	51±	45.0±4	54.0±8
VLDL	26.2±8	28.8±4	19.6±4	-	-	26.2±8	29.8±7	29.9±	35.0±3	55.0±9
S.TG	131±23	144±40	98±12	-	-	131±23	149±9	150±	175±23	275±43
S. Cho	145±34	224±34	201±20	-	-	145±34	189±33	184±	179±33	216±23

T test has been used to compared between control and groups on lipid lowering agents at α< 0.05).Sim = Simvastatin, Ator= Atorvastatin, Clof= Clofibrate, Rusov= Rusovastatin.

The three most common lipid lowering agents used among dyslipidemic non-diabetic patients were simvastatin, atorvastatin and clofibrate. There were no one of lipid lowering agents shown effectiveness in lowering lipid profile as shown in table 6. Since, there were no information on FBS, PPBS and HbA1C in dyslipidemic non-diabetic groups due to lack of the lab results.

Table 6: Effect of lipid lowering agent on serum parameters among diabetes dyslipidemia and dyslipidemic non-diabetes patients:

	Lipid lowering agents								
	No	Sim		Ator		Clof		Rusov	
	Healthy control	Diabetes Dyslipidemia	Dyslipidemia non-DM	Diabetes dyslipidemia	Dyslipidemia non-DM	Diabetes dyslipidemia	Dyslipidemia non-DM	Diabetes dyslipidemia	Dyslipidemia non-DM
mg/dl	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD
FBS	93±13	137±15	-	142±20	-	156±12	-	150±16	-
PPBS	113±12	157±18	-	295±24	-	199±17	-	210±20	-
HBA1C	5.27±1	7.85±1.2	-	7.93±1.1	-	8.38±1.1	-	10.9±1	-
LDL	83.9±5	138.4±20	146.7±11	126.9±9	150.5±10	207.0±20	110.0±20	145.8±11	-

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HDL	49.2±3	48.9±5	30.9±5	52.6±4	37.3±5	45.0±4	55.0±7	54.0±5	-
VLDL	26.2±3	29.5±3	35.4±3	26.5±3	39.9±3	35.0±5	34±4	55.0±6	-
S. TG	131±12	148±14	177±22	132±12	199±26	175±17	150±23	275±26	-
S. Cho	145±14	202±21	247±24	192±14	253±28	179±18	230±30	216±21	-

Sim = Simvastatin, Ator= Atorvastatin, Clof= Clofibrate, Rusov= Rusovastatin.

Further investigated the effect of two effective types of lipid lowering agent (simvastatin and atorvastatin) on serum parameters have been presented in table 7: In compared to other simvastatin doses, 20 mg of simvastatin was greatly significant effect to reduced FBG, PPBS and HbA1C ($P< 0.05$) but fluctuated result has been found on effect different doses on lipid profile in which no convincing result was obtained. Atorvastatin did not show any dose dependent effective on lowering nor blood glucose neither HbA1C. The dose of atorvastatin has been found to have profound and significant effect ($P< 0.05$) on lipid profile and HDL was 40 mg (Table 7).

Table 7: Effect of different doses of lipid lowering agent on serum parameters:

Mg/dl	Simvastatin					Atorvastatin				
	10 mg	20mg	40mg	80mg	100mg	10mg	20mg	40mg	80mg	100mg
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean
FBS	132±12	128±11	140±12	-	-	153±23	168±14	151±17	220±21	-
PPBS	189±18	144±12	157±15	-	-	330±29	260±22	190±23	230±25	-
HBA1C	8.39±1	7.01±1	8.18±1.1	-	-	8.88±1.2	8.20±2	8.86±2	10.0±2	-
LDL	140.7±11	125.6±10	148.0±20	-	-	133.5±11	132.9±17	125.8±14	176.0±12	-
HDL	50.8±8	42.4±4	53.2±4	-	-	42.0±4	59.6±7	50.6±6	38.0±7	-
VLDL	24.5±3	31.8±5	31.1±5	-	-	26.8±3	26.1±5	19.6±5	40.6±5	-
S.TG	123±12	159±9	156±15	-	-	134±13	131±21	98±12	203±26	-
S.Cho	220±21	197±12	208±22	-	-	188±21	195±22	169±14	148±18	-

T test has been used to compared between control and groups on lipid lowering agents at $\alpha< 0.05$).

IV. DISCUSSION:

Lipid lowering agents is considered as cornerstone of prevention of cardiovascular disease. One of the most common risk factors for CVD is diabetes and treatment regimen indicate that most patients with diabetes would benefit from lipid lowering agents. In the present work, investigation of different types of lipid lowering agents with different doses highlighted new finding. As statin a lipid lowering agents administration explored in type 2 diabetes mellitus have been studied extensively in number of studies by Cornell et al [12], Inzucchi et al [13], Wang et al [14]Cui et al [15]. Furthermore, no study conducted or investigated the effect of lipid lowering agents on glycemia in type 1 diabetes mellitus.

In the current work, the lipid lowering agent have been studied include simvastatin, atorvastatin, rosuvastatin and clofibrate because those the most common used clinically in diabetic patients. Simvastatin found lowering fast blood glucose, PPBS and HbA1C in dose 20 mg/day. However, several studies have reported association between statins and diabetic control, but such effects are still receiving controversial and conflicting outcome ranging from adverse, none to beneficial. In diabetic patients, simvastatin has been found to worsen glycemic control and insulin secretion [16-19]. All of aforementioned authors have reported similar results, in which statins worsen or increased glycemic control. Furthermore, still there were data outcome from clinical trials prompted from Food and Drug Administration to add a safety label to statins indicating an increase in HbA1C and fasting blood glucose levels [20]. A number of meta-analyses have demonstrated that that the association of statins with adverse glycemic control is real, though its mechanistic confirmation is still mired with a lot of challenges. Study carried out by Canadian Network for Drug Observational studies revealed that diabetes was highest after starting of statin therapy [21]. Based on the findings of the previous works a potential for statins to disrupt glucose homeostasis should now be considered along with their cardiovascular benefits. The reason beyond these results could be

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due to most studies were either observational studies or uncontrolled trials, have small in size and had short follow-up periods limiting the available evidence to delineate the effect of statins on glucose hemostasis and glycaemic control in diabetes. There were number of studies have suggested that treatment with atorvastatin, but not pitavastatin, may lead to significant deterioration in glycaemic control in patients with diabetes [22].

The present study agree with the previous work in which statin has been shown improve insulin resistance [23].The mechanisms underlying the effect of simvastatin on glycemia are still unclear. However, previous studies have reported that inhibition of glucose-stimulated insulin secretion. Several experimental studies have indicated how simvastatin affects glucose metabolism through different mechanism include inhibit glucose transporter, effect on calcium channel and beta cells[24].

As mentioned above there are two types of lipid lowering agents got significant effect on diabetic glucose hemostasis. In the present work simvastatin and atorvastatin have further investigated and found that generally atorvastatin better worked in lowering serum TG, cholesterol, LDL and VLDL and elevated HDL than simvastatin. In regarding types of diabetes there were difference in which atorvastatin shown better outcome in control serum TG, cholesterol, LDL and VLDL. While such improvement has been noticed in T2DM used either simvastatin or atorvastatin. For diabetes patients statins found to have cornerstones in reduced risk for CVD[25]. Furthermore, single dose of simvastatin 20 mg significantly improve lipid profile in T2DM while 40 mg of atorvastatin shown significant lowering lipid profile and improve HDL in T1DM. In the previous work simvastatin 40 mg/day significant lowering risk of CVD in diabetes patients [26]. Atorvastatin also been used in diabetic patient as mono-therapy and found that significant resulted in a 40% decrease in LDL-C levels with over 80% of patients achieving LDL-C levels less than 100mg/dl[27]. The current work including of dyslipidemic non-diabetic groups in the study in order to exclude any confound factors but there was missing data about FBS, PPBS and HbA1C therefore, it's difficult to make any comparison.Also, there was a time limited due to COVID 19 pandemic. The finding of this study indicated that there was no lipid lowering agent significantly lowering lipid profile in dyslipidemic non-diabetic participants.

Overall, statins particular simvastatin improved glucose hemostasis and HbA1C while atorvastatin worked better in lowering lipid profile and elevated HDL. Regarding types of diabetes, atorvastatin has been found work better in control lipid profile in T1DM. Simvastatin and atorvastatin have similar lowering effect on lipid profile and elevation of HDL therefore lipid lowering agent could add advantages beside their main function in regulation glucose hemostasis and glycemic control.

V. CONCLUSION

The present study demonstrated that, lipid lowering agent particular simvastatin able to improve glycemia include FBS, PPBS and HbA1C in dose of 20 mg/ day. Furthermore, the atorvastatin has been found more effective in reduced serum TG, cholesterol, LDL and VLDL in daily dose 40 mg. The present work also considered some highlighted significant in type 1 diabetes mellitus. Among lipid lowering agents, atorvastatin improved lipid profile and HDL in T1DM. On the other hands, both simvastatin and atorvastatin have similar effect on reduced lipid profile and HDL in T2DM. Overall simvastatin significant reduced FBS, PPBS and HbA1C in both types of diabetes. This data suggested that, single dose of statin be given in the patients as guideline treatment to reduced risk of diabetic induced CVD.

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Nil

Conflicts of interest:
There are no conflicts of interest.

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