

Effect of metformin on blood lipids in patients with diabetes mellitus

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Abstract

Background and objectives: Metformin improves macrovascular complications in people with diabetes mellitus (DM). Although the exact mechanism is not known, metformin has beneficial effects on dyslipidaemia. The aim of the study was to find out if there was an effect of metformin on blood lipids in people with diabetes mellitus.

Method: This was a cross-sectional study which included 80 patients with diabetes mellitus. They were divided into 2 groups – (a) Group 1: on metformin and (b) Group 2: without metformin medication. None of the patients were on any other anti-diabetic medication. All data were obtained from patients' medical records. Individual blood lipids and lipid ratios were compared between two groups.

Result: Group 1 included 42 patients with a mean HbA1c of $7.58 \pm 0.24\%$ taking an average dose of 820.83 ± 60.40 mg/day of metformin. Group 2 consisted of 38 patients with mean HbA1c of $7.58 \pm 0.29\%$. There was no significant difference in individual plasma lipid levels, lipoprotein ratio or frequency of dyslipidaemia between patients taking and not taking metformin ($p > 0.05$). Also, different doses of metformin had no significant effect on the plasma lipid levels.

Conclusion: Metformin did not affect the lipid profile of patients with diabetes mellitus.

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Introduction

There is a multitude of evidence from both observational and intervention studies that metformin improves long-term macrovascular complications in people with type 2 diabetes mellitus [1]. It is associated with a 39% reduction in the incidence of myocardial infarction in diabetes [2]. Although, it is known that this favourable cardiovascular effect is independent of its anti-diabetic action, the exact mechanism is still being studied [3].

Metformin has modest positive effects on dyslipidaemia, inflammation and thrombosis, benefiting vascular function [3]. Some studies have

described that metformin lowers very low density cholesterol (VLDL), triglyceride, low density lipoprotein (LDL), plasminogen activator inhibitors, factor VIII, C-reactive protein, and increases high density lipoprotein (HDL), especially if abnormal [2]. It also stabilizes fibrin and platelets [2]. However, others show no significant effect on blood lipids [4].

The molecular mechanism by which metformin affects the lipid metabolism is still under investigation. Studies have shown that metformin (in a dose of 2300 mg/day) reduces intestinal lipoprotein synthesis and increases glucagon like peptide 1 (GLP1), thereby reducing intestine

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derived triglyceride rich plasma lipids [5]. Metformin modulates cholesterol synthesis by inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) through adenosine monophosphate kinase (AMPK). This action is more pronounced in the intestine than liver, and is seen with high concentrations of metformin [6]. Recent animal studies have shown that metformin inhibits hepatic apoA5 expression, leading to the reduction of the plasma level of triglyceride (TG) in ob/ob mice [7]. Metformin also reduced postprandial hypertriglyceridemia most likely by delaying gastric emptying in mice [8]. Metformin increases cholesterol transport to HDL by up regulation of ATP binding cassette transporter. As a result, there is decreased accumulation of oxidized LDL and foam cells. In addition metformin has been shown to increase secretion of interleukin 10 which is an anti-foam cytokine [9].

Although metformin has proven cardiovascular benefits, the fact that metformin produces clinically significant improvement of blood lipids is not established. Therefore, this study was undertaken to see if there was an effect of metformin on blood lipids in ethnic Bengali people with diabetes mellitus.

Methods

This was a cross-sectional study conducted over a period of 6 months in a hospital. Study population consisted of two groups. Group-1 consisted of people with previously diagnosed diabetes mellitus (DM) taking metformin of any dose and duration. Group-2 comprised of people with DM but not on metformin medication. Group 1 was further divided into those receiving < 1000 mg (Group 1a), and those on \geq 1000 mg metformin (Group 1b) per day. Individuals taking any other anti-diabetic or lipid lowering medication were excluded from the study. Information on patient's age, sex, dose of metformin, duration of diabetes, blood pressure, lipid profile and HbA1c were taken from their medical record. Table-1 shows cut-off values for abnormal lipids used in the study.

All values were expressed as means \pm SE or frequencies. Student's independent t-test and chi-square test were used to compare blood lipids and

lipoprotein ratios between patients with and without metformin medication. One-way ANOVA was used to compare lipids between different doses of metformin. Correlation between lipid level and dose of metformin was analyzed with the Pearson's correlation coefficient test. A p value of \leq 0.05 was taken as significant. The SPSS version 23.0 was used for the statistical analyses.

Table-1: Cut-off values for abnormal blood lipids and lipoprotein ratios [10, 11]

Blood lipid/ lipid ratio	Cut-off for abnormal value
Raised TC	> 220 mg/dl
Raised LDL	>100 mg/dl
Low HDL	<40 mg/dl (male), <50 mg/dl (female)
Raised TG	>150 mg/dl
Non HDL	>130 mg/dl
TC:HDL ratio	>4.5 (male), >4 (female)
LDL:HDL ratio	>3 (male), >2.5(female)
TG:HDL ratio	>2

Note: TC= total cholesterol, TG= triglycerides, HDL=high density lipoprotein, LDL=low density lipoprotein.

Result

A total of 42 cases of DM on metformin were included in Group-1 while Group-2 had 38 DM cases who were not on metformin. The dose of metformin ranged from 500 to 1700 mg per day, with a mean dose of 820.83 ± 60.40 mg per day. All patients had received advice on diet and exercise, though with variable levels of adherence. Both groups were not on any other anti-diabetic or lipid lowering medication. They were of similar age, and had comparable duration and control of diabetes. Patients taking metformin had a greater frequency of hypertension and were on antihypertensive medication including angiotensin converting enzyme inhibitor (ACEI). The baseline characteristics of the two groups are shown in Table-2.

There was no significant difference in individual plasma lipid fractions and lipoprotein ratios between patients with diabetes mellitus taking and not taking metformin ($p>0.05$; Table-3). Also, there

was no significant difference in the frequency of dyslipidaemia among patients with and without metformin medication ($p>0.05$; Table-4). Furthermore, there was no significant difference in plasma lipid levels and lipoprotein ratios as well as in frequencies of dyslipidaemia among patients taking different doses of metformin ($p>0.05$; Table-5 and 6). No correlation between dose of metformin and plasma lipid and lipoprotein ratio was observed by Pearson's correlation analysis ($p>0.05$; Table-7).

Table-2: Baseline characteristics of the study population (n=80)

Characteristics	Group 1 (n=42)	Group 2 (n=38)
Mean \pm SE		
Age (years)	54.74 \pm 1.77	46.97 \pm 1.15
Sex*		
Male	26 (61.90%)	31 (81.58%)
Female	16 (38.10%)	7 (18.42%)
Duration of diabetes (months)	53.69 \pm 8.65	52.45 \pm 7.96
HbA1c (%)	7.58 \pm 0.24	7.58 \pm 0.29
Dose of metformin (mg)	820.83 \pm 60.40	-
Hypertension*	22 (52.38%)	3 (7.89%)

Note: *Expressed in frequency and percentage in parenthesis

Table-3: Lipid profile and lipoprotein ratio of the study population (n=80)

Lipid profile (mg/dl)	Group 1 (n=42)	Group 2 (n=38)	P value
Mean \pm SE			
TC	185.62 \pm 5.35	180.61 \pm 4.79	0.49
LDL	111.12 \pm 5.09	109.47 \pm 4.73	0.82
HDL	39.95 \pm 1.88	38.55 \pm 1.24	0.55
Triglyceride	177.79 \pm 12.45	171.66 \pm 14.24	0.75
Non HDL	145.67 \pm 4.61	142.05 \pm 4.57	0.58
TC:HDL	4.88 \pm 0.17	4.83 \pm 0.16	0.84
LDL:HDL	2.89 \pm 0.14	2.91 \pm 0.14	0.93
TG:HDL	5.03 \pm 0.47	4.77 \pm 0.47	0.70

Note: Student's independent t-test was used to calculate p values.

Table-4: Frequency of dyslipidaemia of the study population (n=80)

Dyslipidaemia	Group 1 (n=42)	Group 2 (n=38)	P value
Frequency n (%)			
Raised Cholesterol	6 (14.3)	4 (10.5)	0.61
Raised LDL	25 (59.5)	23 (60.5)	0.77
Low HDL	22 (52.4)	22 (57.9)	0.62
Raised Triglyceride	24 (57.1)	20 (52.6)	0.67
Non HDL	32 (76.2)	24 (63.2)	0.20
TC:HDL	41 (97.6)	37 (97.4)	0.94
LDL:HDL	26 (63.4)	28 (77.8)	0.17
TG:HDL	37 (88.1)	37 (97.4)	0.12

Note: Chi square/Fisher's Exact test was used to calculate p value. Numbers within parenthesis are percentages over column total.

Table-5: Lipid profile and lipoprotein ratio in patients receiving different doses of metformin and no metformin

Lipid profile (mg/dl)	Group 1a (n=23)	Group 1b (n=19)	Group 2 (n=38)	P value
Mean \pm SE				
Total Cholesterol	185.04 \pm 7.46	186.32 \pm 7.85	180.61 \pm 29.58	0.78
LDL	109.96 \pm 6.43	112.61 \pm 8.39	109.47 \pm 28.36	0.94
HDL	40.91 \pm 2.85	38.79 \pm 2.38	38.55 \pm 7.66	0.67
Triglyceride	171.17 \pm 14.77	185.79 \pm 21.23	171.66 \pm 87.77	0.81
Non HDL	144.13 \pm 6.34	147.53 \pm 6.88	142.05 \pm 28.15	0.80
TC:HDL	4.76 \pm 0.24	5.02 \pm 0.25	4.83 \pm 0.99	0.72
LDL:HDL	2.82 \pm 0.18	2.98 \pm 0.22	2.91 \pm 0.85	0.84
TG:HDL	4.75 \pm 0.55	5.36 \pm 0.82	4.77 \pm 2.90	0.75

Note: One -way ANOVA was used to calculate p values.

Table-6: Comparative frequency of dyslipidaemia in patients receiving different doses of metformin and no metformin

Dyslipidaemia	Group 1a (n=23)	Group 1b (n=19)	Group 2 (n=38)	P value
Frequency n (%)				
Raised Cholesterol	3 (13)	3 (15.8)	4 (10.5)	0.91
Raised LDL	14 (60.9)	11 (57.9)	23 (60.5)	0.89
Low HDL	12 (52.2)	10 (52.6)	22 (57.9)	0.88
Raised Triglyceride	14 (60.9)	10 (52.6)	20 (52.6)	0.84
Non HDL	18 (78.3)	14 (73.7)	24 (63.2)	0.44
TC:HDL	22 (95.7)	19 (100)	37 (97.4)	1
LDL:HDL	15 (65.2)	11 (61.1)	28 (77.8)	0.42
TG:HDL	19 (82.6)	18 (94.7)	37 (97.4)	0.09

Note: Chi square/Fisher's Exact test was used to calculate p value. Numbers within parenthesis are percentages over column total

Table-7: Correlation between dose of metformin and lipid profile/ lipoprotein ratio (n=42)

Blood lipid (mg/dl) / lipid ratio	r	p
TC	0.05	0.77
LDL	-0.003	0.99
HDL	0.10	0.53
TG	0.06	0.70
Non-HDL	0.06	0.61
TC:HDL	0.10	0.93
LDL:HDL	-0.04	0.74
TG:HDL	0.06	0.61

Note: Pearson's correlation was used to calculate the r value

Discussion

Metformin has beneficial effects on cardiovascular complications. Although a number of mechanisms including action on lipids, inflammation, clotting cascade etc. have been proposed, there is still lack of clarity on the exact mechanism. This study looked at the lipid profile in patients with and without metformin, but did not find any association between dyslipidaemia and metformin use.

There was no significant difference in the lipid levels, lipoprotein ratio or frequency of dyslipidaemia between patients using and not using metformin, or taking different doses of metformin. Furthermore, there was no correlation between metformin dose and lipid levels. This

finding is not in accordance with a systematic review of 41 randomized controlled trials that looked into the effect of metformin on lipid profile. This review described significant decrease of plasma triglycerides, total and LDL cholesterol with metformin, but not HDL cholesterol [12]. This beneficial effect of metformin compared to control was independent of glycaemic control (except triglyceride), body mass index, and treatment duration.

There may be several reasons why we did not find any association between lipid profile and metformin use in our study. Studies have shown that metformin reduces intestinal lipoprotein synthesis when used in high doses, of approximately 2300 mg/day [5]. Therefore, an explanation for the lack of effect of metformin on lipid profile may be the low dose (less than 1700 mg/day) used by the patients in this study. Unfortunately, the duration of metformin use was not available from the database. So, we do not know if metformin had sufficient time to affect blood lipids. In randomized controlled trials to see effect of metformin on lipids, metformin was used for at least 6 weeks [12]. Some reports have indicated that the lipid lowering effect of metformin is more pronounced when baseline lipids are markedly elevated [4]. The baseline lipid levels were however not substantially elevated in this study. This may contribute to the lack of difference seen between the two groups. In case of near normal glycaemic control, metformin had no

effect on triglycerides but still affected the total and LDL cholesterol [12]. The HbA1c level was near normal in our study population. This may explain why a difference in triglyceride level was not found. A limitation of this study is its cross-sectional nature with small number of DM cases in both arms. This did not allow us to rigorously control the study to see the effect of introducing metformin on lipid profile. Further prospective study involving larger study population and defined criteria is needed to ascertain the effect of metformin on plasma lipids in ethnic Bengali DM population.

In conclusion, metformin had no effect on lipid profile and lipoprotein ratios in our study population.

Author's contributions

TH designed the study, collected samples, analyzed data, wrote and edited the manuscript. SH was involved in data entry and analysis.

Competing interest

There is no conflict of interest.

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