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Metformin Improves Metabolic Profile in Patients at Risk of Disturbed Metabolic Profile; Dyslipidaemia and Oxidative Stress

Moutaz Shakir*

Head of Training and Development Rizgary Teaching Hospital, Department Clinical Pharmacy, and Imperial College London, UK

Abstract

This studies paper explores the function of metformin in improving lipid profile parameters and lowering cardiovascular risk factors in patients with diabetes mellitus (DM) and ischemic coronary heart disease (IHD). The look at consists of three companies of Iraqi patients: diabetic, diabetic with IHD, and IHD only patients. The parameters evaluated consist of lipid profile, atherogenic index, LDL/HDL ratio, HbA1c degrees, and oxidative pressure markers. The findings advocate that metformin treatment leads to a extensive decrease in LDL cholesterol, an increase in HDL cholesterol, and upgrades in different lipid profile parameters. Furthermore, metformin demonstrates a massive lower in HbA1c stages, indicating its capacity to lessen thrombotic chance. The paper also highlights the antioxidant impact of metformin, as evidenced by a decrease in oxidative stress markers. These effects guide the function of metformin as a secondary choice to lessen the risk of cardiovascular events in patients with DM and IHD.

Keywords: Metformin; Lipid profile; Diabetes mellitus; Ischemic coronary heart disease oxidative pressure markers

Introduction

Diabetes Mellitus (D.M) is a chronic heterogeneous genetic disorder characterized by impaired metabolism of glucose and other energy-yielding fuels, as well as the late development of macro and micro angiopathies. Also there is an associated defect of lipoprotein metabolism referred as lipid triad: elevated serum very low density lipoprotein (VLDL) or TG, small dense LDL (atherogenic) and decrease HDL which is associated with atheroscelropathy and CHD as well as increase redox stress (16). Conclusively D.M is associated with a markedly increased mortality from CHD not explainable by traditional risk factors (19). A high frequency of dyslipidemia which along with hyperglycemia, obesity and hypertension may contribute to accelerated atherosclerosis (20). Atherosclerosis is a progressive inflammatory disorder of the arterial wall which is the most common cause of CAD (The most common (33) risk factors are Sex; men have greater risk of attack than women before menopause Age, 45 and more for male and 55 and more for female.

- Obesity and overweight.
- High Blood Pressure.
- High blood cholesterol specifically increases LDL and decreases HDL.
- Diabetes.

Abdominal obesity increases the risk of CAD Mortality from Cardiovascular disease is almost 50% higher in obese patients than those of average weight and is 90% higher in those with severe obesity (40). Dyslipidemia; The association among high serum cholesterol, LDL, and CAD is causal and independent of other risk factors (41 Recent evidence and epidemiological studies indicate an increase in TG level is a strong independent risk factor (15, 41). Other studies suggested that increase TG may act as synergistically with other lipid abnormalities to increase risk of CAD (43).) In type 2 D.M we have decreased glutathione (GSH) level (58 amelioration of insulin insensitivity by Metformin appears mainly due to enhancement of both non-oxidative metabolism (87) and translocation of glucose transporters from the intra cellular pool to the plasma membrane which are the mechanism operating in the development of I.R Type 2 DM and obesity (88), or it may enhance insulin binding to its receptor, phosphorylation and tyrosine Kinase activity of insulin receptors in vivo. In addition to improvement of lipid profile ; increasing HDL and lowering LDL together with decreased TG besides modest weight loss or at least no weight gain (89). Another advantage is reduction in HbA1c by 1.4-3.3% (90 Also another study shows that Metformin have antioxidant effect (92). Metformin suggested mechanism of action. is through decreasing hepatic glucose production, increase sensitivity to insulin.

This study was designed to: Evaluate the role of metformin in improving some parameters of lipid profile &/or through estimating atherogenic index and LDL/HDL ratio, as a secondary therapeutic goal, to give an idea about reduction in CVRF2). Examine the effect of metformin on HbA1c, since HbA1c is considered as prothrombotic indicator3)Study the effect of metformin on oxidative stress in diabetic and IHD patients separately. Since a variety of factors often acting in concert are associated with an increased risk of atherosclerotic plaque formation in coronary artery diseases (79), so modifiable risk factors should themselves become the target of risk reduction treatment program (80). Three types (81) of risk factors which are: 1) Causal risk factors which include increased LDL-c, decreased HDL-c, Hypertension, and D.M; these are independent R.F. 2) Conditional risk factors, increased concentration of TG-rich lipoprotein, small dense DL particle, LPa and Homocysteine. 3) Predisposing risk factors which are obesity, physical inactivity.

Setting

Seventy five Iraqi patients were classified into three groups

***Corresponding author:** Dr. Moutaz Shakir Hassan, Head of Training and Development Rizgary Teaching Hospital, Department Clinical Pharmacy, and University of Southwales Preventive Cardiovascular Medicine, UK

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depending on their clinical diagnosis as diabetic, diabetic with IHD and solely IHD patients. The patients were attending the out-patients' clinic at Al-Karama Teaching Hospital, Al-Yarmouk Teaching Hospital and the National Diabetes Center.

Materials and Methods

Diagnosis based on clinical symptoms, biochemical investigations, ECG, echo study, angiography, and exercise ECG has been done for special cases. Patients with the following conditions were excluded: Recent MI, Uncontrolled CHF, Liver FailureCRF, Experiencing severe infection, Age above (55) years old for patient with IHD, Taking cimetidine, TG >300 mg /100 ml. Obesity was defined as body mass index extra than 30 kg/m^2; this is known as Quetelet's index calculated as weight in Kg(s) divided by the individual's height in square meters. The patients had been categorised according to their medical prognosis as follows:

Group I: 25 patients with Type 2 DM without IHD were treated by metformin 500 mg thrice daily.

Group II: 25 patients with Type 2 DM affected with IHD were treated by metformin 500 mg thrice daily.

Group III: 25 patients with IHD were treated by metformin 500 mg twice daily.

The patients enrolled in this study take the therapy for three consecutive month's period with monthly evaluation of the intended parameters. At the time of the visit, socioeconomic and demographic information and a full history were obtained using a structured questionnaire (format ECG Study was done for all patients before and after initiating metformin therapy.

Control

Twelve healthy volunteers who were comparable to patients at the following points; BMI and age were selected in this study. The volunteers are without clinical illness and had not received any medication for more than three months before enrollment.

Sample collection

Ten milliliters of venous blood were drawn from every patient and control subject after twelve hours of fasting overnight and this process was performed for the three groups of patients before initiation of therapy and followed by monthly measurements of the same parameters after initiation of metformin therapy. The estimation of lipid profile of group three was deferred for three months if MI episode did not pass three months. The samples were transferred into a clean plain tube, left at room temperature for 30 minutes for clotting, centrifuged, and the serum was separated and divided into two parts: Aliquot of serum was transferred into a plain tube, which was used for measuring glucose, MDA, Cholesterol, HDL-c, and TG. The tubes were stored at 4 C° for no longer than seven days, while serum MDA analysis was done within twenty four hours after sample collection. Whole Blood (2 ml) was transferred into plain tube, which was used for HbA1c analysis. Simple preparation of the samples through hemolyzing the blood and removal of Schiff base; the sample thoroughly mixed and specimens may be stored not more than 7 days at 2-8°C if needed Methods. Low density lipoprotein-cholesterol (LDL-c) was determined by using the Friedwald Equation (98).LDL-c = Total Cholesterol-HDL-c-VLDL. Hemoglobin A1C (HbA1c) is measured by utilizing the principle of ion exchange high performance liquid chromatography (HPLC) for the automatic and accurate separation of HbA1c. The separation of HbA1c is performed rapidly and accurately without interference from Schiff base, lipaemia, or temperature fluctuation. (100).

Electrocardiography (ECG)

An ECG was done for patients who were diagnosed to have IHD and those in group I since patients with type 2 DM may be affected with silent ischemia. Diagnosis and confirmation was done by either tread-mill exercise test or by an angiographic study.

Statistical analysis

The results were expressed as mean ± SD. Students T-test was used to examine the difference in the mean of parameters tested. Pearson correlation (r). P-value of less than (0.05) was considered significant.

Results

Patients before treatment

A demographic presentation of patients were emphasized in Table 1 to show briefly the risk category to which the patient is related which may be present separately or in a heterogeneous manner in the same patient. The body mass index and the age of patients as well as that of control are illustrated in Figure 1. The data in Figure 1 showed that the values of BMI and age of the patients were not significantly different ($p > 0.05$) from that of the control. The glycemic pattern of patients and healthy control were shown and statistically calculated as in Figure 2 below. Lipid profile together with LDL/HDL ratio and atherogenic index, in addition to lipid peroxidation index (serum MDA), and glycemic control index (HbA1c) are presented in Figure 1. The data in Figures 1-10 below showed that the base line level of LDL-c (163.3 mg/100 ml) was highly significant ($P<0.005$) in group III and a significant increment in group I where LDL-c level (152 mg/100 ml) when compared with control level (109 mg/100 ml). On the other hand only in group III significant decline was shown in HDL level

Table 1: Mean ± SD of Body Mass Index (BMI) and Age of different groups of patients and control group before treatment.

Variables	Control level	Base line levels of the patients			Total of all group
BMI (kg/m²)		Group 1	Group 2	Group 3	
	31.8 ± 7.4	33.3♦ ± 5.7	30.7♦ ± 3.8	31.4♦ ± 3.1	32.1♦ ± 4.4
	n=12	n=25	N=25	n=25	
Age (years)					
	50 ± 9.7	48♦ ± 7.9	55.3♦ ± 6.9	47.7♦ ± 5.4	50.25♦ ± 7.4
	n=12	n=25	N=25	n=25	
N: Sample Size, ♦: Non-significant					

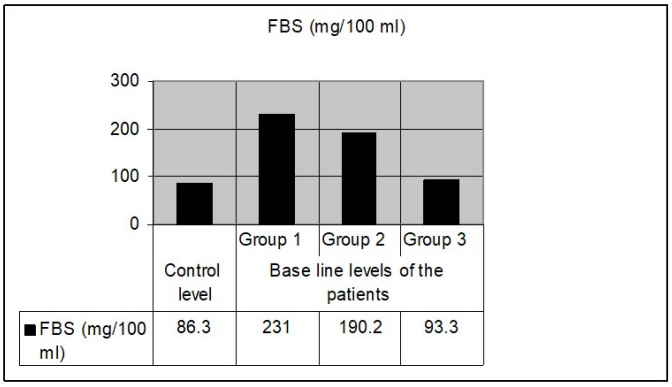
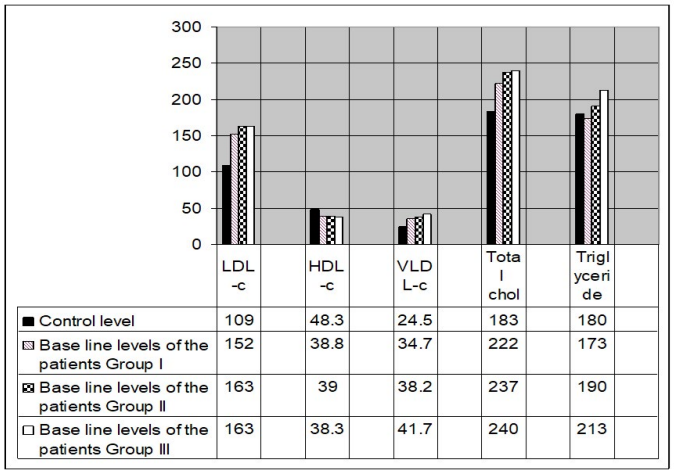
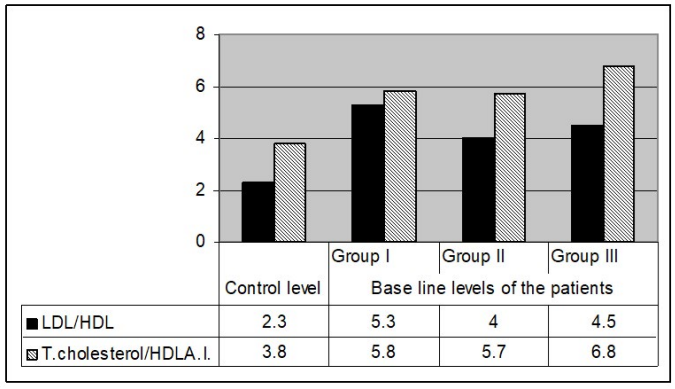


Figure 1: Mean ± SD of Fasting serum glucose of patients and control (n=Sample Size).



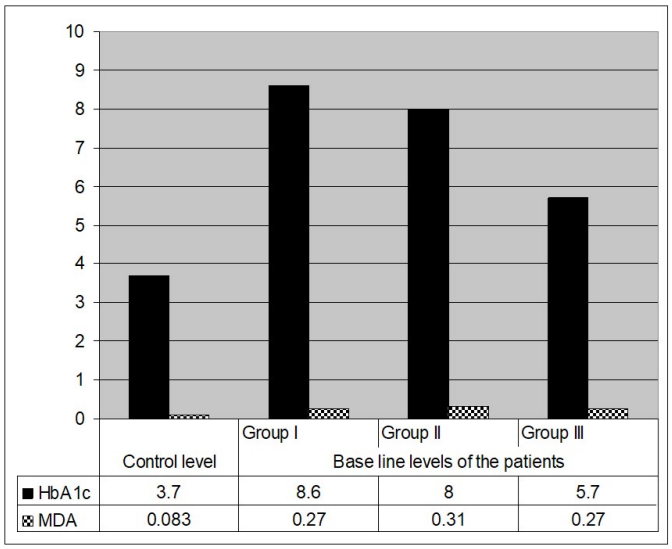
	LDL -c	HDL -c	VLD L-c	Total chol	Triglyceride
Control level	109	48.3	24.5	183	180
Base line levels of the patients Group I	152	38.8	34.7	222	173
Base line levels of the patients Group II	163	39	38.2	237	190
Base line levels of the patients Group III	163	38.3	41.7	240	213

Figure 2: Lipid profile together with LDL/HDL ratio and atherogenic index.



	Control level	Group I	Group II	Group III
LDL/HDL	2.3	5.3	4	4.5
T.cholesterol/HDLA.I.	3.8	5.8	5.7	6.8

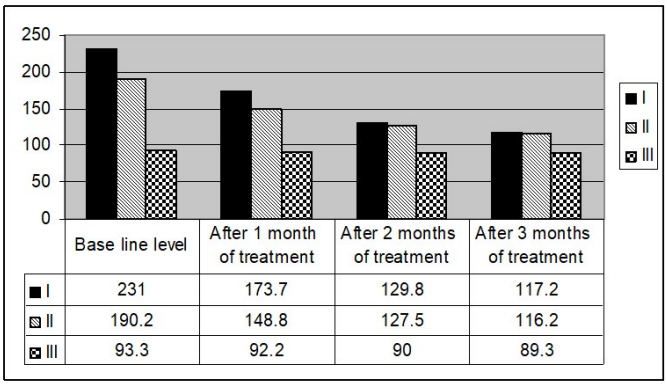
Figure 3: Base line level of LDL-c.



	Control level	Group I	Group II	Group III
HbA1c	3.7	8.6	8	5.7
MDA	0.083	0.27	0.31	0.27

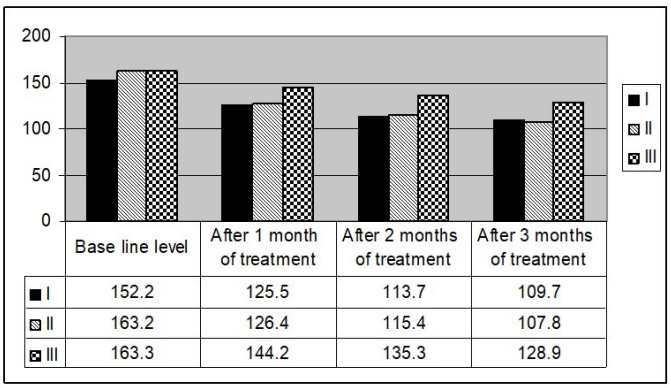
Figure 4: Patients after treatment.

(38.3 mg/100 ml), when compared with control level (48.3 mg/100 ml), whereas serum VLDL-C levels which were (34.7 mg/100 ml for group I, 38.2 mg/100 ml for group II, 41.7 mg/100 ml for group III) showed a significant (P<0.05) rise in all groups of patients when compared with control level (24.5 mg/100 ml). LDL-C/HDL ratio showed a highly significant (P<0.005) increment in group one (5.3), and a significant



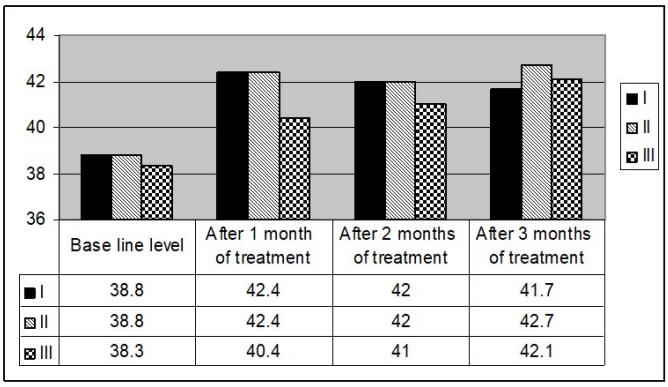
	Base line level	After 1 month of treatment	After 2 months of treatment	After 3 months of treatment
I	231	173.7	129.8	117.2
II	190.2	148.8	127.5	116.2
III	93.3	92.2	90	89.3

Figure 5: Effect of Metformin on Fasting serum glucose level in three study groups.



	Base line level	After 1 month of treatment	After 2 months of treatment	After 3 months of treatment
I	152.2	125.5	113.7	109.7
II	163.2	126.4	115.4	107.8
III	163.3	144.2	135.3	128.9

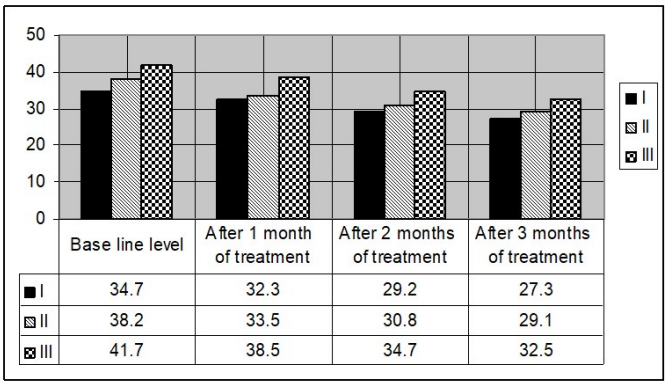
Figure 6: Effect of Metformin on serum LDL-c level in three study groups.



	Base line level	After 1 month of treatment	After 2 months of treatment	After 3 months of treatment
I	38.8	42.4	42	41.7
II	38.8	42.4	42	42.7
III	38.3	40.4	41	42.1

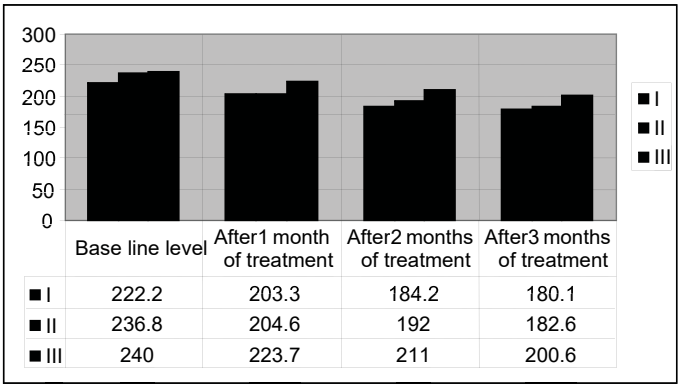
Figure 7: Effect of Metformin on serum HDL-c level in three study groups.

(P<0.05) increment in group II and III (4, 4.5) respectively when compared with control level (2.3). Group I, II, & III showed highly significant (P<0.005) increment in atherogenic index (5.8, 5.7, 6.8), on comparison with base line level (3.8). A highly significant (P<0.005) increment in all groups of patients in HbA1c level (8.6, 8, 5.7) for the three consecutive groups on comparison with control level (3.7). Serum MDA levels (0.27 µmol/L for group I, 0.31 µ mol/L for group II, & 0.27 µ mol/L for group III) showed highly significant (P<0.005) increase in all patients groups when compared to control level (0.083 µ mol/L). LDL levels in the control group are within the desirable range at 109 mg/dL, reflecting a lower risk of cardiovascular diseases. All patient groups exhibit elevated LDL levels compared to the control. Patient Group 1 has a moderate increase, while Patient Groups 2 and 3 show more substantial elevations, potentially indicating a higher



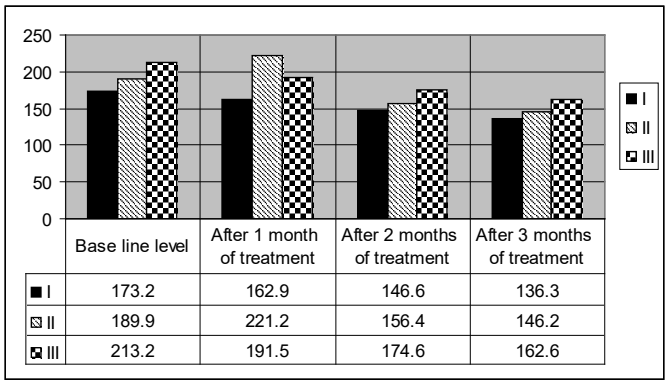
	Base line level	After 1 month of treatment	After 2 months of treatment	After 3 months of treatment
I	34.7	32.3	29.2	27.3
II	38.2	33.5	30.8	29.1
III	41.7	38.5	34.7	32.5

Figure 8: Effect of Metformin on serum VLDL-c level in the three study.



	Base line level	After1 month of treatment	After2 months of treatment	After3 months of treatment
I	222.2	203.3	184.2	180.1
II	236.8	204.6	192	182.6
III	240	223.7	211	200.6

Figure 9: Effect of Metformin on Serum Total Cholesterol in the three study groups.



	Base line level	After 1 month of treatment	After 2 months of treatment	After 3 months of treatment
I	173.2	162.9	146.6	136.3
II	189.9	221.2	156.4	146.2
III	213.2	191.5	174.6	162.6

Figure 10: Effect of Metformin on Serum Triglyceride levels in the three.

risk of atherosclerosis and coronary artery disease. HDL levels in the control group are relatively high at 48.3 mg/dL, indicating a favorable lipid profile and potential protection against cardiovascular issues. HDL levels are lower in all patient groups compared to the control. Patient Group 1 shows a moderate decrease, while Groups 2 and 3 exhibit more pronounced reductions. Lower HDL levels may imply a diminished ability to remove excess cholesterol from the bloodstream. VLDL levels are within a normal range at 24.5 mg/dL in the control group. Patient Group 3 has the highest VLDL levels among the patient groups, indicating a potential higher contribution to total cholesterol from triglycerides. The total cholesterol level in the control group is 183 mg/dL, representing a baseline value. Total cholesterol levels are elevated in all patient groups, with Group 3 having the highest levels. This increase is primarily driven by higher LDL levels, suggesting a potential increased risk of developing atherosclerosis. Triglyceride levels in the control group are 180 mg/dL. Triglyceride levels vary among patient groups, with Group 3 showing the highest levels. Elevated triglycerides may contribute to a pro-atherogenic state and increased cardiovascular risk. The patient groups consistently exhibit less favorable lipid profiles than the control group, characterized by elevated LDL levels, reduced HDL levels, and varying VLDL and total cholesterol levels. The differences in lipid profiles among patient groups suggest potential variations in cardiovascular risk, with Group 3 showing the most unfavorable lipid profile. These findings highlight the importance of monitoring and addressing lipid levels in patient groups to mitigate cardiovascular risks. In the control group, the LDL/HDL ratio 2.3 indicates a relatively balanced proportion of low-density lipoprotein (LDL) to high-density lipoprotein (HDL) cholesterol, suggesting a lower risk of cardiovascular issues. The Atherogenic Index, at 3.8, supports this favorable lipid profile, indicating a potentially lower risk of atherosclerosis. Conversely, in Patient Group 1 at baseline, the elevated LDL/HDL ratio of 5.3 implies an imbalance with a higher proportion of LDL cholesterol, suggesting an increased risk of atherosclerosis and cardiovascular diseases. The Atherogenic Index of 5.8 aligns with this observation, reinforcing the heightened cardiovascular risk in this group. In Patient Group 2, although the LDL/HDL ratio is lower at 4.0, it still indicates an elevated risk compared to the control, with a relatively higher LDL cholesterol level in proportion to HDL. The Atherogenic Index of 5.7 mirrors this trend, pointing towards an increased risk of atherosclerosis. Patient Group 3, with an LDL/HDL ratio of 4.5 and the highest Atherogenic Index of 6.8 among the groups, suggests a continued elevation in cardiovascular risk. While specific values for Total Cholesterol/HDL ratio are not provided, the analysis of LDL/HDL ratio and Atherogenic Index collectively indicates that patient groups may have an elevated risk of atherosclerosis compared to the control group. The patients enrolled in this study received metformin therapy for a three consecutive months during which a monthly estimation of anthropometric measure (BMI), and biochemical estimation of the selected parameters. In addition to an ECG, ECHO study and/or angiographic study was done for selected patients. Patients with IHD were investigated by ECG showed no deterioration and no frequent ischemic attacks during the period of treatment.

The biochemical changes in all patients' groups

Fasting serum glucose levels were shown in Figure 5 for type II diabetic (group I), type II diabetic with IHD (group II) and IHD (group III). Highly significant decrement in FBS ($p \leq 0.005$) during all three months after initiation of treatment by metformin in group I & group II while it is not significant ($P > 0.05$) in group III when compared with their base line levels

Serum low density lipoprotein (LDL-C) in three study groups

The effect of metformin therapy on serum levels of serum LDL-C in the three enrolled groups was shown**.** The data in Figure 6 showed a highly significant reduction in serum LDL-c level ($p \leq 0.005$) in the three enrolled groups after treatment by metformin during the three months treatment when compared with base line level.

Serum high density lipoprotein (HDL) in the three study groups

In Figure 7 the effect of metformin during the three consecutive months in all groups was shown below: In group I & II significant increment in HDL levels was recognized in Figure 7 at first, second &

third month (p≤0. 05) of treatment by metformin, while it was highly significant (p≤0. 005) for group III in the three months of treatment when compared with their base line levels.

Serum very low density lipoprotein (VLDL-C) in the three study groups

The results of the effect of metformin therapy on serum VLDL-c level in the three study groups were illustrated in Figure 8. In group I there was no significant decrement (P >0.05) in serum. VLDL-c level at first month whereas there was a significant (p ≤ 0.05) decrement in serum VLDL-c level at the second month, and a highly significant decrement (p ≤ 0.005) at third month of metformin therapy when compared with base line level as in Figure 8 above. In group II & III, there was a significant decrement (p ≤ 0.05), in serum VLDL-C level at first month while it was highly significant (p ≤ 0.005), at third month of metformin therapy when compared with base line level.

Serum total cholesterol (TC) in the three study groups

Figure 9 showed metformin therapeutic effect on serum total cholesterol in the three study groups A highly significant decline (p≤0. 005) in serum total cholesterol level during all three months of metformin treatment in all the three study groups when compared to their base linelevels as illustrated in Figure 9.

Serum triglyceride (TG) in the three study groups

The effect of metformin on serum Triglyceride levels were shown in Figure 10 below for the entire study group. Serum Triglyceride level showed a significant (p≤0. 05) decline at second month of treatment while it was highly significant (p≤0. 005) decline at third month of metformin therapy when compared with base line level in group I. In group II a highly significant (p≤0. 005) decline was shown during the second and third month of metformin treatment. In group I & II no significant (p>0.05) change occur at first month of treatment. In group III a highly significant (p≤0. 005) decline was shown during all the three months of treatment as in Figure 10.

Serum LDL-C/HDL ratio in the three study groups

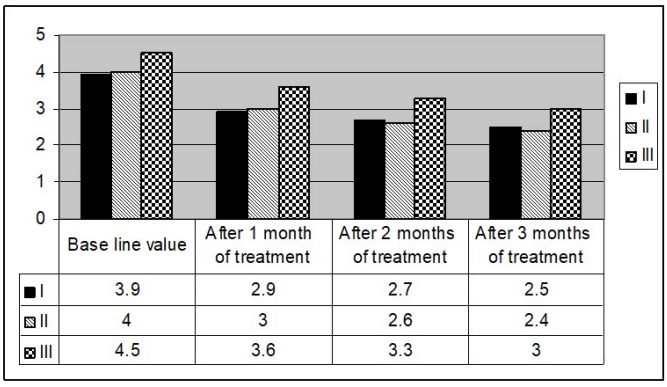
In the Figure 11 below the effect of metformin on serum LDL/HDL ratio was shown during the period of treatment in all the enrolled groups in this study. This Figure 11 showed that there was a highly significant decline in LDL/HDL ratio (p≤0. 005) after initiation of treatment by metformin along the three months period of treatment for all the three study groups when compared with their base line levels.

Serum TC/HDL ratio (Atherogenic Index) in the three study groups

Metformin therapeutic effect on serum total cholesterol/HDL ratio was well illustrated in Figure 12 in the three study groups. This Figure 12 shows that there was a highly significant reduction in TC/HDL ratio (p≤0. 005) when compared with base line value for all the groups enrolled in this study.

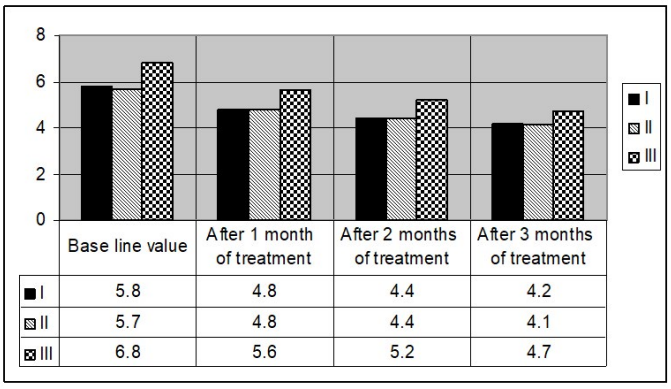
Glycosylated hemoglobin (HbA1c) in the three study groups

The effect of metformin on glycemic index (HbA1c) was shown in the Figure 12 below: Figure 13 showed a highly significant decrement in HbA1c level (p≤0. 005) when compared with base line levels after commencing of therapy with metformin in the three enrolled groups in this study except, a non-significant change (p>0.05) was shown at the first month of metformin therapy in group II. A highly significant reduction in HbA1c level which were (7.9, 7.3, &7.0), in group I when



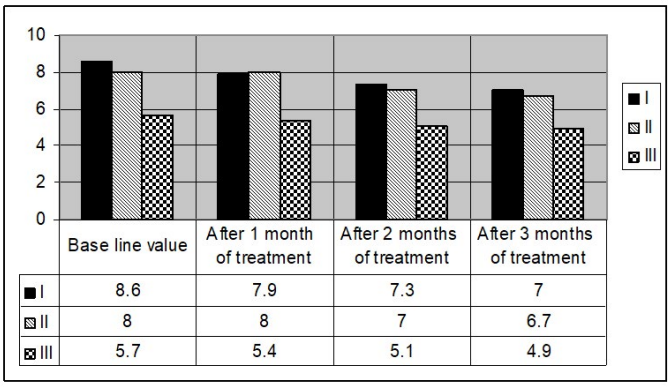
	Base line value	After 1 month of treatment	After 2 months of treatment	After 3 months of treatment
I	3.9	2.9	2.7	2.5
II	4	3	2.6	2.4
III	4.5	3.6	3.3	3

Figure 11: Effect of Metformin on serum LDL-C/HDL ratio in the three study groups.



	Base line value	After 1 month of treatment	After 2 months of treatment	After 3 months of treatment
I	5.8	4.8	4.4	4.2
II	5.7	4.8	4.4	4.1
III	6.8	5.6	5.2	4.7

Figure 12: Effect of Metformin on serum TC/HDL ratio in the three study groups.



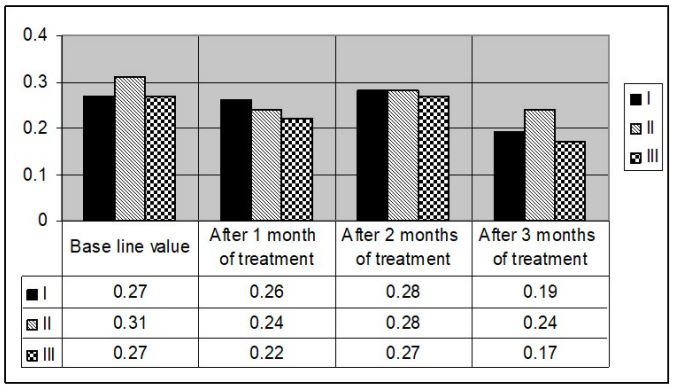
	Base line value	After 1 month of treatment	After 2 months of treatment	After 3 months of treatment
I	8.6	7.9	7.3	7
II	8	8	7	6.7
III	5.7	5.4	5.1	4.9

Figure 13: Effect of Metformin on (HbA1c) in the three study group.

compared with base line level (8.6) after initiation of metformin therapy during the three consecutive months, while in group II, there was no significant change (p>0.05) at first month whereas a highly significant reduction (p≤ 0.005) in HbA1c levels which were (7.0, 7.6) was shown after metformin therapy at second and third month when compared to base line level (8.0) as shown in figure (4.39, 4.40) respectively. A highly significant reduction (p≤ 0.005) in HbA1c levels which were (5.4, 5.1, &4.9) for group III, when compared to base line levels (5.7), as shown in Figure 3, after initiation of metformin therapy during all the three months period.

HbA1c levels are expressed in percentages

Serum malonaldialdehyde (MDA)



	Base line value	After 1 month of treatment	After 2 months of treatment	After 3 months of treatment
I	0.27	0.26	0.28	0.19
II	0.31	0.24	0.28	0.24
III	0.27	0.22	0.27	0.17

Figure 14: Effect of Metformin on Serum Malondialdehyde in the three study groups.

The effect of metformin on serum MDA level was shown in Figure 14 in all the study groups. Only at third month post commencing metformin therapy, there was a highly significant ($p \leq 0.005$) change in serum MDA level while a non-significant ($p > 0.05$) reduction was shown during first and second month of metformin therapy, in group I, & III when compared to their base line levels. In group II a highly significant ($p \leq 0.005$) reduction was shown at first and third month post commencing metformin therapy while a non-significant ($p > 0.05$) change was shown at second month when compared to base line level as recognized in Figure 14.

Discussion

A number of contributory pathophysiological defects among the three groups enrolled in this study. Since D.M is considered as a vascular disorder and IHD in which the focus point is the vessels to which the plaque or atheroma was stuck. In addition to a comparative scenario of mediators that appear to be relative to a great extent; whether the mediator is inflammatory, metabolic and/or hormonal which are involved in coronary heart disease, so on this comparative basis we built our background of selecting these groups. The dyslipidemic pattern in all groups was in favor of increased atherogenesis as reflected from increased LDL/HDL ratio and atherogenic index as revealed in Figures 3 and 4 which are considered as more sensitive marker of CAD than HDL-c alone(14,103). Groups which are presented in the current study have an increased LDL-c level; as shown in Figures 3 and 2 which carries a risk of CHD as emphasized by NCEP guidelines (104). The significant reduction in HDL-c level shown in present study in Group III has an implication of reduced anti-inflammatory, anti-oxidant and anti-atherogenic effect of HDL (49). On the other hand, the levels of HDL-c in group I &II showed no decrement which is similar to other studies (18). The reported significant increase in VLDL-c in all groups which play apart in atherosclerosis and CHD AS Shown in Figure 3. TG and TC showed non-significant statistical difference among the three study groups and control as shown in Table 1 From the above observations, we realized that all the study groups showed a mixture of borderline and /or high risk serum concentrations that signify a familial combined dyslipidemia or dyslipidemia of diabetes, and in accordance with the last reports we focused not only on isolated parameters of lipid profile because it does not confer protection for at-risk patients, so a secondary therapeutic goal was chosen which is LDL /HDL ratio and/or AI (17)Another study hypothesized that HbA1c is a prothrombotic indicator (77). Hence it has been used a prothrombotic indicator among the three groups. Furthermore, an increased concentration of serum MDA, as shown in Figure 4 complicates the picture of dyslipidemia and gives an accelerated pattern of macrovascular disease. The increased level of serum MDA in diabetic & IHD patients is documented in other studies (17,106). Moreover, increased oxidative stress as measured by indices of lipid peroxidation and protein Oxidation has been shown to be increased in both types of D.M (109). Together with increased body of evidence that indicate the role of ROS as a causative agents for many diseases like atherosclerosis (110,111,112,113).

The effect of metformin on serum low density lipoprotein

The level of serum LDL-c showed a highly significant ($p \leq 0.005$) decline in the three groups of patients during the whole period of treatment by Metformin as shown in Figure 5. This reduction gives a chance toward reduced level of atherogenic lipoprotein, hence CVRF is somewhat ameliorated, although the validity of this finding has been questioned (119).; but for non-diabetic patients group III; the highly significant reduction in serum LDL-c level need to be viewed in relation to the criteria of cardiovascular metabolic syndrome since the National Cholesterol Education Program (NCEP) guidelines (101) define this syndrome as the presence of three or more of the followings: abdominal obesity, TG >150 mg/100 ml, an HDL level < 40 mg/100 ml in men and less than 50 in women and systolic blood pressure >130 mmHg. In group III, the first three criteria were met, hence metformin can play a role as an insulin sensitizer (87, 88) which may carry a possible explanation of how Metformin reduce serum LDL-c levels in obese non-diabetic IHD patients.

The effect of metformin on serum high density

The results in the present study showed a significant ($p \leq 0.05$) increment in serum HDL-c level in group I in the three consecutive months when compared with base line level. A significant ($p \leq 0.05$) increment has been achieved in group II at first and second month of metformin therapy, while it was highly significant at third month as shown in Figure 6. These results are in agreement with the results in other studies (120). A noteworthy phenomenon has been noticed at the second month of metformin therapy in group I&II, which reveals that the action of metformin is temporary as in Table 1. This goes hand by hand with the suggestion of other workers who reported that the effect of metformin may be to some extent transient and some cellular adaptation may occur during more prolonged therapy (121). The patients of group III are not diabetic in this study but since they were obese, they may be considered as pre-diabetic patients (122), in addition they met the criteria of cardiovascular metabolic syndrome. This increment confers an increased cardiovascular protection due to the role of serum HDL in reverse cholesterol transfer and the ability of HDL in preventing LDL-c oxidation. On the other hand, in a large epidemiological studies, when other variables are adjusted, a suggestion arose that for each 1 mg/100 ml increase in S.HDL-c, CAD risk decreases by 2% in men And 3% in women (123,124).

The effect of metformin on serum very low density

The decreasing manner of serum VLDL-c level in group I was significant ($p \leq 0.05$) at second month, highly significant ($p \leq 0.005$) at third month, whereas it was not significant ($p > 0.05$) in the first month post commencing of metformin treatment as shown in Table 1. In patients of group II and III, serum VLDL-c level showed a significant ($p \leq 0.05$) decrease at first month while it was highly significant ($p \leq 0.005$) at second and third month post commencing metformin therapy when compared to base line value as shown in Figure 1. The achieved decrement manner goes with other studies which realized that metformin action needs a time to be established (88). In type 2

D.M patients, metformin results in inhibition of VLDL synthesis by liver (125) in non-diabetic patients (group III), this obtained reduction in VLDL level suggest that these patients are again fulfill the first three criteria of the NCEP to be considered as patients with metabolic syndrome so metformin can take a role to reduce serum VLDL-c since insulin resistance is a metabolic feature of this syndrome (126).

The effect of metformin on serum total cholesterol

All the three study groups showed a highly significant ($p \leq 0.005$) decline in serum TC level along the three consecutive months of metformin therapy as shown in Figure2. In group I and II, the results are in agreement with other studies (91). Whereas in participants of group III patients; whom met the metabolic syndrome criteria; the reduction in serum TC level achieved by metformin might be emphasized since metformin is hypolipidemic agent. Concerning CVRF reduction, studies indicate that each 1 mg/100 ml reduction in serum TC level gives 1% reduction in CVRF (127).

The effect of metformin on serum triglyceride

In group I, no significant ($p > 0.05$) decline in serum TG level at first month, while the decline in serum TG level is significant at second month ($p \leq 0.05$) and highly significant ($p \leq 0.005$) at third month of metformin treatment. In group II only a highly significant ($p \leq 0.005$) decline in serum TG level was obtained at second and third month of metformin therapy. Those two diabetic groups show the same manner of reduction in serum TG level of other studies (89) The participants of the third group showed a highly significant ($p \leq 0.05$) reduction all over the three consecutive months of metformin treatment which can be attributed to inhibition of catecholamine-stimulated lipolysis (128) which may contribute to decrease Serum TG level. The associated abnormalities with increased Serum TG often include insulin resistance, decrease HDL, diabetes and obesity, as well as a hypercoagulable state together with increased serum marker of inflammation seen in metabolic syndrome (NCEP guidelines). This achieved reduction considered as a recommendation target by the NCEP (101).

The effect of metformin on serum LDL\HDL ratio& on total cholesterol\HDL ratio

Serum LDL\HDL ratio showed a highly significant ($p \leq 0.005$) decline in group I, II, & III as shown in Figure 3 during all the three months of metformin treatment. The increased LDL\HDL ratio implies a state of atherogenic dyslipidemia (129) so the reduction achieved by metformin may offer a degree of reduction in CVRF. Along the three months of treatment by metformin AI levels showed a highly significant ($p \leq 0.005$) decrement as shown in Figure 4, which gave a place for metformin to be used if a secondary therapeutic goal is targeted by the therapist since some patients may show a normal level of other parameters in lipid profile but clinically they are at-risk patients according to American Association of Clinical Endocrinologists (AACE) guidelines (129).

The effect of metformin on glycosylated hemoglobin

As shown in Figure 1, the HbA1c levels showed a highly significant ($p \leq 0.005$) decline in HbA1c levels for all the three study groups along all the three months period of treatment by metformin except at first month of treatment in group II as shown in Figure 1 This implies that metformin need a time to do its action (88)Another implication is that the achieved reduction in HbA1c reveals that the patients were compliant with the study regimen(29), On the other hand, as supposed by some researchers (105), that HbA1c may be a prothrombotic indicator, so a sound is gained for metformin to ameliorate this supposed prothrombotic indicator

The effect of metformin on serum malondialdehyde

In group I & III the highly significant ($p \leq 0.005$) reduction in serum MDA level is only at third month of metformin therapy when compared with base line level as shown in Table 1 and Figure 1. This may be attributed to transient action of metformin &\or cellular adaptation besides of an n observed increase in serum MDA after two months of metformin treatment in group I. In group II, a highly significant($p \leq 0.005$) reduction serum MDA was achieved at first & third month as shown in Figures 10-14 after metformin treatment, while it is not significant ($p > 0.05$) at second month which may be attributed to cellular adaptation mentioned above This achieved reduction in oxidative stress may support the results in other studies which reveals an antioxidant effect for metformin (130) but in this study the effect may be transient & need to be augmented by the addition of another antioxidant such as vitamin E. The amelioration achieved in lipid profile can be used in favors of reducing CVRF thus it may offer some degree of cardioprotection in both diabetic and non-diabetic patients. The antioxidant effect of metformin need an extension of the period of the study in order to examine the unpredicted effect of metformin on oxidative stress and/or investigate its antioxidant effect on total antioxidant status (TAS). Compared to these previous studies, PHARYSPOR offers unique insights using a large-scale real-world dataset derived from EMRs. This approach minimizes the limitations associated with controlled clinical trials and enhances the generalizability of the findings to diverse patient populations. By focusing on the Indian context, the study recognizes the role of regional variations in disease patterns and antibiotic resistance profiles. Furthermore, PHARYSPOR extends the scope of the investigation to include the tolerability of the prescribed antibiotics, recognizing that treatment success also depends on the patient's adherence to therapy. As such, the study is poised to contribute to evidence-based pharyngitis management substantially, ultimately informing clinical decision-making and improving patient outcomes. The study's real-world design enhances the generalizability of the findings, reflecting the diversity of patients and healthcare settings. However, limitations include the retrospective nature of data collection, potential biases in EMR documentation, and the absence of a placebo-controlled group. Future research could involve prospective studies with larger patient cohorts and standardized data collection methods.

Conclusions

The findings of this studies paper imply that metformin treatment has beneficial results on lipid profile parameters and cardiovascular chance elements in patients with DM and IHD. Metformin has been shown to lead to a sizeable lower in LDL cholesterol, an growth in HDL cholesterol, and upgrades in different lipid profile markers. These changes recommend a potential reduction in atherogenic risk and safety towards cardiovascular activities. Additionally, metformin demonstrates a full-size lower in HbA1c stages, which may additionally make a contribution to a lower thrombotic risk. The antioxidant impact of metformin as proven by a reduction in oxidative strain markers has been highlighted by using the study. The findings support the use of metformin to lessen cardiovascular threat in sufferers with DM and IHD, the use must but be a secondary therapeutic option. Further research and medical trials ought to be performed to verify these effects and explore the long-time period outcomes of metformin remedy on cardiovascular effects in such patients.

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