# The effect of glipizide, metformin and rosiglitazone on nontraditional cardiovascular risk factors in newly diagnosed patients with type 2 diabetes mellitus

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Background: Diabetes mellitus (DM) is recognized as a major risk factor for cardiovascular disease (CVD). Traditional cardiovascular risk factors (CVRFs) alone cannot explain excess risk for CVD associated with DM; nontraditional CVRFs also may play an important role. Aim: To study the effects of glipizide, metformin and rosiglitazone on traditional [lipid profile, lipoprotein Lp(a)] and nontraditional CVRFs [homocysteine (Hcy), soluble Vascular Cell Adhesion Molecule (sVCAM-1), malonyldialdehyde (MDA) and nitric oxide (NO) levels]. Setting and Design: An open-label, randomized, parallel group study was conducted in the departments of pharmacology, internal medicine and biochemistry of Lady Hardinge Medical College. Materials and Methods: Ninety newly diagnosed type 2 DM patients were randomly assigned to glipizide, metformin or rosiglitazone treatment daily for a duration of 12 weeks. If needed, the dosages were titrated upward to achieve fasting plasma glucose <126 mg /dL. Plasma glucose, glycosylated hemoglobin (HbA1c), lipid profile, body mass index (BMI), Lp(a), Hcy, sVCAM-1, MDA and NO were estimated both before and after treatment. Statistical Analysis: Data were analyzed using paired Student's t-test within each group. Results and Conclusion: All the three drugs led to significant decrease in HbA1c, fasting and postprandial plasma glucose levels. Glipizide lowered body weight, BMI, total cholesterol (P < 0.05), low density lipoprotein cholesterol (LDL-C) (P < 0.01) and MDA levels (P < 0.05). Metformin reduced body weight (P < 0.01), BMI (P < 0.01), LDL-C, very low density lipoprotein cholesterol (VLDL-C) and improved high density lipoprotein cholesterol (HDL-C); however, it raised Hcy levels (P < 0.01). Rosiglitazone treatment increased

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body weight (P < 0.01) and LDL-C (P < 0.01); however, it improved HDL-C (P < 0.01) and decreased sVCAM-1 (P < 0.05) and MDA (P < 0.05) levels.

**KEY WORDS:** Glipizide, homocysteine, lipid profile, cardiovascular risk factors, malonyldialdehyde, metformin, nitric oxide, rosiglitazone, soluble Vascular Cell Adhesion Molecule

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# Introduction

American Heart Association has designated diabetes mellitus (DM) as a major risk factor for cardiovascular disease (CVD).<sup>[1]</sup> It is estimated that cardiovascular complications are responsible for majority of deaths among people with type 2 diabetes. There is twofold to fourfold increased risk of coronary heart disease (CHD), stroke and peripheral vascular events in type 2 diabetics. A part of this excess risk relates to an increased prevalence of established risk factors such as obesity, dyslipidemia and hypertension in these patients.<sup>[2]</sup> The importance of these factors has been reviewed in United Kingdom Prospective Diabetes Study (UKPDS).<sup>[3]</sup> Many studies have suggested that only traditional risk factors cannot explain the excess risk for CHD associated with diabetes; so, nonconventional risk factors may play an important role.<sup>[4,5]</sup> In several studies, individuals with diabetes have shown unfavorable lipid profile, altered plasma levels of oxidative stress markers like nitric oxide (NO),[6,7] malonyldialdehyde (MDA)<sup>[6,8]</sup> and atherogenic substances, that is, soluble Vascular Cell Adhesion Molecule (sVCAM-1),<sup>[9]</sup> lipoprotein [Lp(a)]<sup>[10,11]</sup> and homocysteine (Hcy).<sup>[12,13]</sup> So, glucose lowering agents that cause a substantial improvement in these parameters should also cause uniform reduction in cardiovascular risk.

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Studies have shown that glipizide,<sup>[14]</sup> metformin<sup>[15]</sup> and rosiglitazone<sup>[16-18]</sup> have significant effects on traditional and nontraditional cardiovascular risk factors (CVRFs) like sVCAM-1,<sup>[9]</sup> Lp(a),<sup>[10,19]</sup> Hcy,<sup>[12,19,20]</sup> MDA<sup>[21]</sup> and NO<sup>[22]</sup> levels in type 2 diabetics but these reports are few and inconclusive. Hence, we compared the effect of three antidiabetic drugs, that is, glipizide, metformin and rosiglitazone, which differ in their primary mechanism of action, on both traditional and nontraditional CVRFs in newly diagnosed type 2 diabetes patients achieving almost equivalent levels of plasma glucose.

# **Materials and Methods**

An open-label, randomized, parallel group study for a duration of 12 weeks was conducted in the departments of pharmacology, internal medicine and biochemistry of Lady Hardinge Medical College, Delhi.

## Subjects

Newly diagnosed type 2 DM patients, aged at least 30 years, were enrolled in the study. Patients were excluded from the study if any of the following conditions was present: history of serious or hypersensitivity reactions to any of the three drugs glipizide, metformin and rosiglitazone; patients with uncontrolled hypertension, heart failure (New York Heart Association (NYHA) class IV), recent unstable angina, myocardial infarction, coronary artery bypass surgery or angioplasty within previous 2 months; transient ischemic attacks, cerebrovascular accident; pregnant, lactating women or those using oral contraceptives; endocrine disorders other than diabetes; renal insufficiency and chronic alcoholism. An informed consent was obtained from all the patients. Patients were free to withdraw their consent to participate at any time during the study period. The study protocol was approved by Institutional Ethics Committee.

General physical and systemic examination was done, and blood glucose level and glycosylated hemoglobin A1c (HbA1c) level were measured to determine patient eligibility to participate in the study. Eligible patients were further investigated for complete lipid profile, Lp(a), Hcy, sVCAM-1 and markers of oxidative stress, that is, NO and MDA levels. Study patients were randomized to receive treatment with glipizide 5–15 mg once daily (OD) or twice daily (BD), metformin 500–1500 mg BD or thrice daily (TDS) or rosiglitazone 4–8 mg OD/BD, and were asked to visit the diabetes clinic for follow ups on day 7, 15, 30, 60 and 90. If fasting plasma glucose (FPG) levels were consistently greater than 126 mg/dL after 2–4 weeks, the dosages of drugs were titrated upward. Adherence to regimen and diet was reinforced. At every follow-up visit, fasting blood glucose was estimated and body weight and blood pressure were also recorded. Patients not controlled on maximum dosages were put on combination therapies and were excluded from the study. All the baseline investigations, that is serum lipid profile [total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), very low density lipoprotein cholesterol (VLDL-C)], Lp(a), MDA, NO, sVCAM-1, Hcy were repeated after 12 weeks and compared with baseline values. The patients were also monitored for any adverse drug effects during the course of study.

#### Measurements

TC was estimated by a timed end-point method of Richmond<sup>[23]</sup> and TGs were estimated by a timed end-point diazo method of Jacobs *et al.*<sup>[24]</sup> HDL cholesterol kit was used for the estimation of HDL cholesterol by polyethylene glycol (PEG) precipitation and enzymatic method. Absorbances were read at 520 nm wavelength using green filter. LDL-C and VLDL-C were estimated using the Friedwald's formula as follows:

LDL-C = TC - (HDL-C + VLDL-C), where VLDL-C = TG/5.

sVCAM-1 (Diclone, Tepnel Life Science, Wythenshawe, UK), NO (Oxis International, Baverly Hills, USA), Lp(a) (DRG International, USA), Hcy (Diazyme Laboratory, Poway, USA) and HbA1c were analyzed using the hemoglobin enzymatic assay kit (Diazyme Laboratory). MDA levels were measured spectrophotometrically using thiobarbutaric acid, as described by Dildar *et al* (1998).

#### **Statistical Analysis**

Analysis of baseline and follow-up end-points within the glipizide, metformin and rosiglitazone treatment groups was accomplished using paired Student's *t*-test [SPSS version 10.0 software (SPSS Inc., Chicago, IL, USA]. Statistical significance was considered at P < 0.05.

## **Results**

Ninety out of 94 recruited patients of type 2 DM completed the study. Four patients were excluded due to poor glycemic control by monotherapies. The mean age of patients in glipizide, metformin and rosiglitazone groups were  $49.5 \pm 10.0$  years,  $50.9 \pm 9.37$  years and  $50.5 \pm 9.32$  years, respectively.

Metformin significantly reduced the mean body weight and body mass index (BMI) (P < 0.01) in contrast to significant weight gain with rosiglitazone (P < 0.05) after 12 weeks of treatment, whereas glipizide reduced mean body weight and BMI, but not significantly [Table 1]. All the study drugs (glipizide, metformin and rosiglitazone) significantly reduced the baseline mean fasting and postprandial plasma glucose levels after 12 weeks of treatment (P < 0.001) [Table 1]. The baseline mean HbA1c levels reduced significantly on administration of glipizide (P < 0.05), metformin (P < 0.01) and rosiglitazone (P < 0.001) [Table 1].

Metformin showed significant favorable effect on lipid profile, that is, decrease in TGs (P < 0.01), TC (P < 0.01), LDL-C (P < 0.01) and VLDL-C (P < 0.01) and increase in HDL-C (P < 0.001). Glipizide also showed beneficial effects by reducing TC (P < 0.05) and LDL-C (P < 0.01), whereas it showed no effect on HDL-C, TG and VLDL-C. Rosiglitazone showed partially favorable effect on lipid profile by significantly increasing HDL-C (P < 0.01) but it also increased TC (P < 0.01) and LDL-C (P < 0.01) levels [Table 2]. The baseline mean Lp(a) levels in all study groups reduced slightly but not to the level of significance [Table 2].

1470 + 211

198.7 ± 24.4

 $8.59 \pm 0.23$ 

111.2 ± 6.7\*\*\*

155.1 ± 12.8\*\*\*

8.25 ± 0.77\*\*

FPG (g/dL)

HbA1c (%)

PPPG (g/dL)

Rosiglitazone showed beneficial effect on nontraditional CVRFs by significantly decreasing mean sVCAM-1 (P < 0.05) and MDA (P < 0.05) levels. Hcy levels decreased and NO levels increased slightly, but not to the level of significance after 12 weeks of treatment. Glipizide treatment led to significant decrease only in MDA levels (P < 0.05). Metformin did not show any significant effects on sVCAM-1, MDA and NO except an increase in Hcy levels (P < 0.01) [Table 2].

All the treatments were well tolerated and no serious adverse event occurred. The side-effect profile varied between the treatment groups, glipizide (5), rosiglitazone (3) and metformin (14). Commonly reported adverse drug reactions were pedal edema (3) with rosiglitazone; anorexia (3), abdominal discomfort (6), vomiting (2), diarrhea (3) with metformin; and nausea (3), vomiting (1) and sweating (1) with glipizide.

#### Discussion

121.0 ± 10.5\*\*\*

179.0 ± 22.7\*\*\*

7.60 ± 0.47\*\*\*

Our study showed that glipizide, metformin and rosiglitazone reduce FPG and HbA1c in newly diagnosed

 $161.9 \pm 37.6$ 

 $229.4 \pm 56.4$ 

 $8.3 \pm 0.92$ 

116.9 ± 13.5\*\*\*

174.4 ± 19.6\*\*\*

7.4 ± 0.66\*\*\*

Table 1: Comparison of body weight, BMI, plasma glucose levels and HbA1c of study patients before and after treatment										
Parameters	Glipizide treatment (mean ± SD)		Metformin treatment (mean ± SD)		Rosiglitazone treatment (mean ± SD)					
	Baseline	After 12 weeks	Baseline	After 12 weeks	Baseline	After 12 weeks				
Body weight (kg)	60.4 ± 9.5	57.9 ± 8.93	60.5 ± 7.61	59.2 ± 6.96**	56.4 ± 7.54	57.6 ± 6.82*				
BMI (kg/m <sup>2</sup> )	25.7 ± 4.02	24.6 ± 3.81	25.7 ± 3.22	25.1 ± 3.00**	24.3 ± 3.10	24.7 ± 2.71*				

156.1 ± 43.9

 $229.7 \pm 64.3$ 

8.71 ± 0.71

Comparison of values within same group at baseline and after 12 weeks. *P* values are reported for comparison by paired student's *t*-test comparing differences attributable to treatment, \*P < 0.05; \*\*P < 0.01; \*\*P < 0.001, PPPG: postprandial plasma glucose

	Glipizide treatment		Metformin treatment		Rosiglitazone treatment					
	Baseline	After 12 weeks	Baseline	After 12 weeks	Baseline	After 12 weeks				
TC (g/dL)	147.8 ± 43.8	136.3 ± 33.5*	138.3 ± 43.3	122.9 ± 21.3**	154.2 ± 40.4	169.5 ± 35.1**				
TG (g/dL)	116.0 ± 83.4	115.2 ± 65.8	119.4 ± 56.2	101.5 ± 32.8**	154.6 ± 40.0	156.3 ± 52.3				
HDL-C (g/dL)	45.4 ± 5.53	45.6 ± 3.92	$43.6 \pm 4.03$	46.4 ± 3.07***	$43.0 \pm 4.45$	44.4 ± 3.26**				
LDL-C (g/dL)	79.2 ± 38.0	67.5 ± 30.9*	70.8 ± 35.0	56.12 ± 16.8**	80.2 ± 37.3	93.8 ± 33.8**				
VLDL-C (g/dL)	23.2 ± 16.6	23.0 ± 13.1	23.8 ± 11.2	20.3 ± 6.56**	30.9 ± 15.65	31.2 ± 10.46				
Lp(a) (mg/dL)	17.6 ± 14.8	16.2 ± 11.3	20.5 ± 13.1	20.0 ± 13.2	20.9 ± 12.8	20.8 ± 12.09				
sVCAM-1 (ng/mL)	$566.5 \pm 74.4$	563.0 ± 74.4	597.36 ± 67.8	590.4 ± 65.8	588.8 ± 70.3	573.2 ± 58.1*				
Hcy (µM/L)	12.3 ± 1.87	12.5 ± 1.75	13.0 ± 1.99	13.4 ± 1.95**	12.5 ± 1.96	12.1 ± 1.37				
MDA (µM/L)	0.54 ± 0.12*	0.51 ± 0.12	0.60 ± 0.11	$0.59 \pm 0.09$	$0.65 \pm 0.16$	0.61 ± 0.11*				
NO levels (µM/L)	15.6 ± 1.51	15.7 ± 1.17	15.5 ± 1.44	16.0 ± 0.97	14.9 ± 1.59	15.3 ± 1.64				

Table 2: Comparison of lipid profile, inflammatory and oxidative stress markers in all the study patients before and after 12 weeks of treatment

*P* values are reported for comparison by paired student's *t*-test comparing differences attributable to treatment. Comparison of values within same group at baseline and after 12 weeks, \*P < 0.05; \*\*P < 0.01; \*\*P < 0.001

type 2 DM similar to that shown by several other studies.<sup>[25,26]</sup> Rosiglitazone and glipizide treatments cause weight gain, whereas metformin reduces weight as reported by several studies.<sup>[16,27,28]</sup> Weight gain in DM patients is associated with increased cardiovascular risk; however, the increased risk may depend upon the amount and type of weight gain (i.e., adipose tissue, lean body mass and fluid accumulation) and distribution of fat (central/peripheral). Weight gain with thiazolidinediones (TZDs) may be either due to increase in adipose tissue, lean body mass or fluid accumulation. TZDs also cause redistribution of fat from visceral to subcutaneous tissues, which may be an explanation for the simultaneous improvement in glycemia and insulin resistance observed with increase in body weight.<sup>[29,30]</sup> As visceral adiposity was not assessed in our study, it could not be determined whether relationships existed between body fat distribution and the differential effects of rosiglitazone and metformin on glycemic control and insulin sensitivity.

In our study, all the treatments revealed variable effects on lipid profiles. Significant increase in HDL levels were observed with rosiglitazone and metformin, which appears to be the primary lipid effects of these drugs as reported in previous studies.<sup>[16,31,32]</sup> Glipizide and metformin displayed significant decrease in LDL levels, which are similar to earlier observations.[25-27] Significant increase in LDL levels by rosiglitazone could be the result of both increases in LDL particle size and number, which is not considered very harmful.<sup>[16]</sup> Increase in TC in this group can be explained by increase in both LDL-C and HDL-C levels; however, greater decrease in LDL cholesterol in metformin and glipizide groups can be the reason of decrease in TC in these groups. Only metformin therapy significantly reduced TG and VLDL levels, which are in accordance with an earlier study.<sup>[33]</sup> These above findings suggest better role of metformin in improving the lipid profile.

The serum level of Lp(a) is an independent indicator of development of cardiovascular risk, the latter correlating with its accumulation in the vascular wall.<sup>[34]</sup> It has been reported that diabetic patients have higher levels of Lp(a).<sup>[35]</sup> In our study, baseline serum Lp(a) levels in all the study groups were higher than normal (0–3 mg/dL); however, none of the drugs altered Lp(a) levels. Absence of a decrease in Lp(a) by rosiglitazone is also supported by Derosa *et al*,<sup>[19]</sup> who showed that pioglitazone decreased but rosiglitazone did not. Further, longterm studies are warranted to determine the effect of

hypoglycemic drugs on Lp(a) levels in diabetic patients.

In the present study, rosiglitazone significantly reduced sVCAM-1 levels, whereas metformin and glipizide did not cause any significant changes [Table 2]. This suggests rosiglitazone's anti-inflammatory effect and potential antiatherogenic property. Several studies have shown that TZDs dampen the inflammatory response in macrophages,<sup>[16,33,36]</sup> reduce macrophage homing to atherosclerotic plaque and also limit chronic inflammation by inhibiting the induced expression of circulating sVCAM-1.<sup>[17,18,33]</sup> A study by Agarwal (2006) has also reported similar anti-inflammatory effect of pioglitazone in men with advanced diabetic nephropathy.<sup>[14]</sup>

We observed variable effects of treatments on Hcy levels. Metformin caused an increase in Hcy levels similar to that reported in studies of Killicdag *et al*<sup>[20]</sup> and Wulffelé *et al*,<sup>[37]</sup> which can be explained by simultaneous decrease in folic acid and vitamin B<sub>12</sub> levels by metformin.<sup>[20]</sup> The decrease in Hcy levels by rosiglitazone is supported by Derosa *et al*.<sup>[19]</sup> However, significant decrease in Hcy level in their study may be due to longer duration of their study (1 year) as compared to our study (12 weeks). Absence of a change in Hcy levels with glipizide is similar to that reported by Agarwal.<sup>[14]</sup> So, it can be concluded that adding Hcy lowering drugs (i.e., folic acid and vitamin B<sub>12</sub>) to metformin may help in reducing cardiovascular risk in diabetics.

MDA is a very toxic byproduct formed from lipid oxidation derived free radicals, and it reacts both reversibly and irreversibly with proteins and phospholipids causing stiffening of collagen of cardiovascular system, which leads to resistance to remodeling. In diabetes, MDA formation is increased by glycation products that stimulate breakdown of the lipids.<sup>[38]</sup> In our study, glipizide and rosiglitazone decreased MDA levels, whereas metformin did not, which is in accordance with the findings of Agarwal.<sup>[14]</sup> In another study, glibenclamide did not alter MDA levels, whereas gliclazide lowered the same.<sup>[21]</sup> There are no reports in literature about the effect of rosiglitazone on MDA levels. So, more studies should be conducted to know the exact relationship between DM treatment and MDA levels.

NO is a gaseous lipophilic free radical cellular messenger, and plays an important role in protection against the onset and progression of CVD by regulating vascular tone, inhibition of platelet aggregation and

leukocyte adhesion, and prevention of smooth muscle proliferation.<sup>[39]</sup> NO levels have been reported to be lower in diabetics than in control subjects.<sup>[13,40]</sup> In our study, NO levels increased in all the study groups though not significantly. There are no reports in literature about the effect of any of the study drugs on NO levels; however, a study by Wang *et al.*<sup>[41]</sup> has reported that rosiglitazone decreased asymmetric dimethylarginine (ADMA) level, a NO synthetase inhibitor. This supports the finding of an increase in NO levels in our study. Long-term studies are required to unveil the effect of rosiglitazone on NO and ADMA levels.

To summarize, our prospective randomized, parallel group study signifies rosiglitazone's anti-inflammatory and antioxidant effects as it reduced sVCAM-1 and MDA levels, respectively, suggesting its potential antiatherogenic role. However, our study does not suggest any direct antiatherogenic effect of metformin and glipizide as these did not lower serum sVCAM-1 levels. Beneficial role of metformin in obese type 2 diabetics is similar to that reported in previous studies, as it reduces body weight, BMI and improves the lipid profile.

Limitations of this study include its small sample size and open label design. Selection bias also limits the generalizability of our findings since only those patients without cardiac contraindications to rosiglitazone were included. Given these limitations and potential biases, our preliminary results require confirmation in larger prospective studies of longer durations.

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