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Original Research Article

Effect of Metformin on Lipid profile of type II Diabetes

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ABSTRACT

Introduction: Insulin resistance and type 2 diabetes are associated with a clustering of interrelated plasma lipid and lipoprotein abnormalities, which include reduced HDL cholesterol, increased levels of LDL, TGs, Total cholesterol and VLDL. Each of these dyslipidaemic features is associated with an increased risk of cardiovascular disease. Metformin is used with a proper diet and exercise program and possibly with other medications to control high blood sugar. It is used in patients with type 2 diabetes. Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems. Proper control of diabetes may also lessen your risk of a heart attack or stroke. Metformin works by helping to restore your body's proper response to the insulin you naturally produce. It also decreases the amount of sugar that your liver makes and that intestines absorb.

Material and Methods: 200 subjects were selected from diabetic type II patients who are on treatment of only metformin(1500mg/daily). The parameters were performed after 3 months of treatment. FBS, Insulin, TC, TGs, HDL-C, LDL-C and VLDL –C were measured.

Results: The results of this study showed improved levels of FBS. The total cholesterol, triglycerides, LDL-C and VLDL-C were reduced significantly($P<0.05$). the HDL-C levels were increased significantly after treatment with metformin.

Conclusion: The results were clearly indicated that beneficial effect of metformin on lipid profile of type II diabetes. Hence concluded that metformin having the ability to correct dyslipidaemia in type II diabetic patients.

KEY WORDS: Type II Diabetes, Metformin, Dyslipidaemia, Lipid profile.

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BACKGROUND

Dyslipidemia is one of the major cardiovascular disease risk factors and plays an important role in the progress of atherosclerosis, the underlying pathology of CVD. The prevalence of dyslipidemia in type 2 diabetes is double with respect to the general population. These are more complex abnormalities that are caused by the interrelation among obesity and insulin resistance [1]. The characteristic features of diabetic dyslipidaemia are a high plasma triglyceride concentration, low HDL cholesterol concentration and increased concentration of small dense LDL-cholesterol particles. The lipid changes associated with diabetes mellitus are attributed to increased free fatty acid flux secondary to insulin resistance. The availability of multiple lipid-lowering drugs and supplements provides new opportunities for patients to achieve target lipid levels [2]. Patients with diabetes mellitus are at higher risk for cardiovascular events than those without diabetes. Furthermore, patients with diabetes have a characteristic 'lipid triad' of low high-density lipoprotein-cholesterol levels, high triglyceride levels and normal or slightly raised low-density lipoprotein-cholesterol levels, with a preponderance of small, dense LDL-C particles. Current guidelines on preventing cardiovascular disease recognize the need not only to reduce LDL-C levels, but also to increase HDL-C and decrease triglyceride levels in diabetic patients [3].

Alterations in lipid metabolism are recognized concomitant symptoms of diabetes mellitus. It is believed that even before the development of overt diabetes, insulin resistance and a prediabetic state impair the mechanism that suppresses fatty acid release from adipose tissue after food intake [4]. The resultant excess of free fatty acids leads to increased concentrations of triglyceride (TG)–rich particles (very low-density lipoproteins and chylomicrons) and TG enrichment of high- and low-density lipoprotein (HDL and LDL), affecting virtually every lipid and lipoprotein variable [5]. The end result is a dyslipidaemia that is characterized by elevated TG levels, the generation of small, dense LDL particles, and reduced HDL cholesterol (HDL-C) concentrations.

This combination of features is known by many designations, including atherogenic dyslipidaemia, dyslipidaemia of insulin resistance or the atherogenic lipoprotein phenotype. It contributes to the 2 to 4 times excess risk for cardiovascular disease observed in patients with type 2 diabetes mellitus compared with nondiabetic individuals [6]. It is also increasingly recognized that the presence of diabetes places most patients at the same near-term risk for a coronary event as that of a patient with existing coronary heart disease (CHD). Diabetes incidence is increasing rapidly in the general population, drawing attention to the role of atherogenic dyslipidaemia in the evolution of CHD among these patients. Attempts to correlate CHD incidence among patients with diabetes with the classic coronary risk factors, showed that these risk factors account for only 25% to 30% of the excess risk for CHD [7]. The degree to which hyperglycemia makes up the difference in risk observed in the diabetic compared with the nondiabetic population is unresolved. Aggressive glycemic control substantially reduces the incidence of microvascular complications of diabetes, such as retinopathy and nephropathy, however the benefits in terms of macrovascular complications, including CHD, have been more difficult to document. Lowering LDL-C levels with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors significantly reduces the risk for major coronary events in patients with diabetes [8].

The discovery of metformin began with the synthesis of galegine-like compounds derived from *Gallega officinalis*, a plant traditionally employed in Europe as a drug for diabetes treatment for centuries [9]. Metformin acts primarily at the liver by reducing glucose output and secondarily, by augmenting glucose uptake in the peripheral tissues, chiefly muscle. These effects are mediated by the activation of an upstream kinase, liver kinase B1 (LKB-1), which in turn regulates the downstream kinase adenosine monophosphatase protein kinase (AMPK). AMPK phosphorylates a transcriptional co-activator, transducer of regulated CREB protein 2 (TORC2), resulting in its inactivation which consequently downregulates transcriptional events that promote synthesis of gluconeog-

enic enzymes [10]. Inhibition of mitochondrial respiration has also been proposed to contribute to the reduction of gluconeogenesis since it reduces the energy supply required for this process [11]. Metformin's efficacy, security profile, benefic cardiovascular and metabolic effects, and its capacity to be associated with other antidiabetic agents makes this drug the first glucose lowering agent of choice when treating patients with type 2 diabetes mellitus (TDM2). Developing countries are expected to shoulder the majority of the burden of diabetes [12]. One of the main contributing factors to this burden is the Western lifestyle which promotes obesity and sedentarism [13]. Impaired glucose tolerance and impaired fasting glucose statuses are associated with increased and varying risk of developing type 2 diabetes mellitus. Impaired glucose tolerance has been associated with an increased risk of cardiovascular events and may determine an increased mortality risk. The association of impaired fasting glucose with cardiovascular events, however, has not been well established [14]. When lifestyle interventi-ons fail or are not feasible, pharmac-ological therapy may be an important resource to prevent type 2 diabetes. Several different drug classes have been studied for this purpose[15]. The present study is concentrated on effect of metformin on lipid profile of type II diabetes.

MATERIALS AND METHODS

200 subjects were selected from diabetic type II patients who are on treatment of only metformin(1500mg/daily). The parameters were performed after 3 months of treatment. FBS, TC, TGs, HDL-C, LDL-C and VLDL –C were measured. Initially the patients were selected without any treatment and found diabetes, later we have started treated them with metformin(1500mg/daily). After three months of their treatment we have measured all above mentioned parameters and compared with initial values. The ANOVA performed with posthoc t –test. The values expressed with mean and SD.

RESULTS

The fasting blood samples were collected 0 day of treatment, 45th day of treatment and 90th day of treatment. The results were clearly indicated there was significance difference after treatment with metformin, the results showed corrected dyslipidaemia after 45 days and after 90 days it has come to almost near to normal. In results observed that decrease in fasting blood glucose, total cholesterol, LDL- C and TGs. HDL-C levels were increased significantly after treatment (Table -1).

Table 1: showing the lipid profile and FBS levels in metformin treated patients.

Parameter	Groups			
	0 day of treatment	45th day of treatment	90th day of treatment	P
FBS (mg/dl)	182.45+ 15.64^{a}	137.62+ 18.72^{b}	112.64+ 20.39^{c}	0.0009
TC (mg/dl)	209.72+ 30.76^{a}	192.64+ 21.65^{b}	165.72+ 7.65^{c}	0.0001
HDL- C (mg/dl)	24.11+ 4.56^{a}	29.57+7.60^{b}	32.76+ 8.92^{c}	0.0001
LDL- C (mg/dl)	147.34+ 20.28^{a}	130.15+ 6.43^{b}	105.42+ 3.51^{c}	0.0001
TGs (mg/dl)	188.92+ 24.93^{a}	161.73+ 15.47^{b}	148.61+ 5.74^{c}	0.0001

DISCUSSION

The present study showed the beneficial effect clearly after the 45 th day of treatment and 90 days of treatment. It is showed clearly metformin treatment is clearly indicating that after the treatment diabetic patient corrected the dyslipidaemia. A meta-analysis of 41 randomized, controlled evaluations ofmetformin of at least 6-week duration showed significant reductions in total cholesterol, LDL cholesterol and triglycerides in patients randomized to metformin relative to comparator treatments[16], HDL-cholesterol was rarely improved by metformin treatment. Some non-randomized studies have demonstrated significant reductions in free fatty acids following treatment with metformin[17]. In nondiabetic persons and those with impaired glucose tolerance randomized in the Diabetes Prevention Program[18], the metformin effect on lipid profile was modest and generally smaller than the effect of the intensive lifestyle intervention included in this trial. It suggests that reductions in the risk of macrovascular endpoints with metformin, showed in the UK Prospective Diabetes Study[19], is associated with other mechanisms, not only the effects on lipids. Metformin also decreases oxidative stress, inhibits lipid peroxidation of LDL and HDL, and the production of the superoxide free radical in platelets[20]. Metformin may reduce

the production of advanced glycation endproducts indirectly, by reduction of hyperglycemia, and directly by an insulininde pendent mechanism[21]. Experimental studies Suggest that metformin may inhibit the binding of monocytes to cultured vascular cells and differentiation of monocytes into macrophages and their transformation into foam cells [22].

In consistent with many studies, significant improvement in glycemic parameters (FBG) was seen over a short period of 8-12 weeks in moderately severe, newly diagnosed diabetic patients treated with either glimepiride, metformin or combination, when compared with pre-treatment[23,24,25]. The improvements in glycaemic parameters with glimepiride and metformin were similar, while combination produced a lower degree of reduction with respect to the change in FBG [26,27,28]. The previous studies approved that glimepiride increases insulin sensitivity at peripheral target sites and improve glycemic control in newly diagnosed diabetic subjects, The extra-pancreatic effects of glimepiride made its combination with metformin more effective in improving glycemic control by reducing glucose level[29,30]. Newly diagnosed type 2 diabetic patients, at baseline, show varying features with respect to lipid profile, present study agreed with previous studies; demonstrated that metformin as monotherapy reduced TC, LDL-C, significant decrease in TG levels [31,32,33] and increase serum HDL-C level. Therefore, our results concluded that metformin used in diabetic treatment improves lipid profile in agreement with previous studies.

REFERENCES

[1]. Singh G, Kumar A.K. A Study of Lipid Profile in Type 2 Diabetic Punjabi population. Journal of Exercise Science and Physiotherapy, Vol. 8, No. 1: 7-10, 201.

[2]. Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. Nat Clin Pract Endocrinol Metab. 2009 Mar;5(3):150-9.

[3]. Steiner G. A new perspective in the treatment of dyslipidemia : can fenofibrate offer unique benefits in the treatment of type 2 diabetes mellitus?. Treat Endocrinol. 2005;4(5):311-7.

[4]. Frayn KN Insulin resistance and lipid metabolism. Curr Opin Lipidol. 1993;4197- 204.

[5]. Kreisberg RA Diabetic dyslipidemia. Am J Cardiol. 1998;8267U- 73U.

[6]. American Diabetes Association, Clinical practice recommendations 1998: management of dyslipidemia in adults with diabetes [position statement]. Diabetes Care. 1998;21 (suppl) S36- S39.

[7]. Pyorala KLaakso MUusitupa M Diabetes and atherosclerosis: an epidemiologic view. Diabetes Metab Res Rev. 1987;3463- 524.

[8]. Grundy SMBenjamin IJBurke GL et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation. 1999;1001134- 1146.

[9]. Godarzi MO, Brier-Ash M: Metformin revisited: re-evaluation of its properties and role in the pharmacopoeia of modern antidiabetic agents. Diabetes Obes Metab. 2005, 5: 654-665.

[10]. Shaw RJ, Lamia KA, Vasquez D: The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. Science. 2005, 310: 1642-1646. 10.1126/science.1120781.

[11]. El-Mir MY, Nogueira V, Fontaine E: Dimethyl biguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. J Biol Chem. 2000, 275: 223-228. 10.1074/jbc.275.1.223.

[12]. Wild S, Roglic G, Green A, Sicree R, King H: Global prevalence of diabetes. Estimates for the year 2000 and projections for 2030. Diabetes Care. 2004, 27: 1047-1053. 10.2337/diacare.27.5.1047.

[13]. Guillies C, Abram KR, Lambert PC, Cooper NJ, Sutton AJ: Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ. 2007, 334: 299-10.1136/bmj.39063.689375.55.

[14]. Petersen J, Mc Guire D: Impaired glucose tolerance and impaired fasting glucose – a review of diagnosis, clinical implications and management. Diabetes Vasc Dis Res. 2005, 2 (1): 9-15. 10.3132/dvdr.2005.007.

[15]. Lilian Beatriz, Aguayo Rojas, Marilia Brito Gomes. Metformin: an old but still the best treatment for type 2 diabetes Diabetology & Metabolic Syndrome20135:6.

[16]. Wulffele MG, Kooy A, de Zeeuw D, Stehouwer CD, Gansevoort RT. The effect of metformin on blood pressure, plasma cholesterol and triglycerides in type 2 diabetes mellitus: a systematic review. J Int Med 2004;256:1-14.

[17]. Manzella D, Grella R, Esposito K, Giugliano D, Barbagallo M, Paliosso G. Blood pressure and cardiac autonomic nervous system in obese type 2 diabetic patients: effect of metformin administration. Am J Hypert 2004;17:223-227.

[18]. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention of metformin. N Engl J Med 2002;346:393-403.

[19]. UK Prospective Diabetes study Group. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854-865.

[20]. Gargiulo P, Caccese D, Pignatelli P, Brufani C, De Vito F, Marino R, et al. Metformin decreases platelet superoxide anion production in diabetic patients. Diabetes Metab Res Rev 2002;18:156159.
[21]. Beisswenger P, Ruggiero-Lopez, D. Metformin inhibition of glycation processes. Diabetes Metab 2003;29:6S95-6S103.
[22]. Mamputu JC, Wiernsperger NF, Reiner G. Antiatherogenic properties of metformin: the experimental evidence. Diabetes Metab 2003;29:6S71-6S76.
[23]. Weitgasser R. Effects of glimepiride on HbA1c and body weight in Type 2 diabetes: results of a 1.5-year follow-up study, Diabetes research and clinical practice. 2003;61:13-19.
[24]. Inglea P and Taleleb G. Effects of metformin in combination with glimepiride on HbA1c and body mass index inIndian patients with type 2 diabetes mellitus, Journal of Pharmacy Research. 2010; 3(9): 2177-2179.
[25]. Min W. Effect of short-term intensive therapy with glimepiride and metformin in newly diagnosed type 2 diabetic patients J. South Med Univ. 2011;31:564-566.
[26]. Charpentier G, Fleury F, Kabir M, Vaur L and Halimi S., Improved glycaemic control by addition of glimepiride to metformin monotherapy in Type 2 diabetic patients, Diabetic Medicine. 2001;18:828-834.
[27]. Moses R. Effect of repaglinide addition to metformin monotherapy onglycemic control in patients with type 2 diabetes. Diabetes Care. 1999;22:119-124.
[28]. Ramachandran A, Snehalatha C, Salini J and Vijay V. Use of Glimepiride and Insulin Sensitizers in the Treatment of Type 2 Diabetes. A Study in Indians, JAPI. 2004;52:459-463.
[29]. Haupt E, Knick B, Koschinsky T, Liebermeister H, Schneider J and Hirche H. Oral antidiabetic combination therapy with sulphonylureas and metformin. Diabetes Metab. 1991;17:224-31.
[30]. Riddle M. Combining sulfonylureas and other oral agents. Am J Med. 2000;108(Suppl) 6a:15S-22S.
[31]. Salpeter SR, Greyber E, Pasternak GA and Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis. Arch Intern Med. 2003;163:2594.
[32]. Kim HJ. Effects of rosiglitazone and metformin on inflammatory markers and adipokines: decrease in interleukin-18 is an independent factor for the improvement of homeostasis model assessment-beta in type 2 diabetes mellitus,Clin. Endocrinol. (Oxf.) 2007;66(2):282-9.
[33]. Riccio A, Del Prato S, De Kreutzenberg SV and Tiengo A. Glucose and lipid metabolism in non-insulin dependent diabetes: effect of metformin. Diabetes Metab. 1991;17:180–184.

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