Effects of metformin, glyburide and their combination on lipid profile in NIDDM patients

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الخلاصة

داء السكري يلعب دورا هاما في إضعاف بطانة الأوعية الدموية واختلال نسبة الدهون وتصلب الشرايين. من المهم تقييم آثار مضادات السكر عن طريق الفم على اختلال الدهون بالإضافة إلى آثار خفض مستوى السكر في الدم لأن هذا قد يوفر نهجا أفضل في العلاج والوقاية من داء السكري. قمت بدراسة آثار كل من الأدوية المضادة لداء السكري والتي تعطى عن طريق الفم وهي: غليبورايد، الميتفورمين، والجمع بينهما على 111 مريض بداء السكري النوع الثاني الذين تتراوح أعمارهم بين 39-58 عاما، وتعاملت لمدة عامين مع خطوط العلاج المختلفة، ومقارنة النتائج مع الأصحاء. قمت بدراسة نسبة كل من (TC-C)، (TG-C)، (HDL-C)،(VLDL-C)، و (LDL-C) في مصل الدم كمؤشر لتأثير الأدوية المستخدمة على اختلال نسبة الدهون.لاحظت انخفاض مستوى أل TC-C، TG-C، LDL-C، و -VLDLوارتفاع مستوى أل HDL-C لدى المرضى الذين استخدمت ميتفورمين وحده، وغليبورايد / ميتفورمين ، في حين استخدام الغليبورايد وحده أنتج ارتفاع ملحوظ بمستوى TC- LDL-C,VLDL-C,TG-C وانخفاض بمستوى HDL-C. في الختام عقار الميتفورمين، والجمع بين الغليبورايد/الميتفورمين تعطي حماية اكثرمن اختلال نسبة الدهون المصاحبة لداء السكري النوع الثاني وتصلب الشرايين بالمقارنة من استخدام عقار الغليبورايد لوحده

Abstract

Background and Objectives: DM plays an important role in the endothelial dysfunction and vascular complications like dyslipidemia and atherosclerosis., It is important now a day to evaluate the dyslipidemic effects of oral hypoglycemic drugs in addition to blood glucose lowering effects, since this may provides a better treatment approach and participates in the prevention of complications of DM.

Patients and Methods : We studied the dyslipidemic effects of glyburide, metformin, and their combination on (111) NIDDM patients aged from 39 – 58 years, treated for two years with different treatment lines and compared the results with healthy controls. Serum (TC-C), (TG-C),(HDL-C),(VLDL-C), and (LDL-C) levels were estimated as a marker of dyslipidemia in the serum utilizing lipid profile kit.

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Results: Serum TC-C, TG-C, LDL-C, and VLDL-C levels significantly reduced and serum HDL-C levels significantly elevated in patients used metformin alone and glyburide / metformin combination therapy so, maintained serum lipid profiles at levels closer to that of controls, while patients used glyburide as monotherapy significantly increased serum TG-C, TC-C, VLDL-C, and LDL-C levels and significantly decreased serum HDL-C levels in comparison to control group.

Conclusion: Metformin / glyburide combination therapy and metformin monotherapy provide better protection against dyslipidemia associated with NIDDM patients than glyburide used alone, and hence better prevention of complications like atherosclerosis.

Key words: DM : Diabetes mellitus TC-C : total cholesterol, TG-C : Triglyceride, HDL-C : High density lipoprotein, LDL-C : Low density lipoprotein, VLDL-C : Very low density lipoprotein, NIDDM : non-insulin dependent diabetes mellitus.

Introduction

Diabetes mellitus is one of the most important non communicable diseases and is second only to hypertension in terms of public health significance. [1, 2]. In diabetes many factors may affect blood lipid levels, this is because carbohydrates and lipid metabolism are interrelated to each other if there is any disorder in carbohydrate metabolism [3], it also leads to disorders in lipid metabolism, so, there is high concentration of cholesterol, triglycerides, and LDL-C and due to this there is reduction in HDL-C cholesterol levels[4]. The development of cardiovascular disease in non-insulin dependent DM (NIDDM) or (Type II DM) is often predicted by several factors which include central obesity, hypertriglyceridemia, elevated low-density lipoprotein (LDL-C) levels, and hypertension [5]. Hypertriglyceremia and low high-density liopoproteinaemia (HDL-C) are two components of the atherogenic profile seen in DM [6]. Elevated low density lipoprotein (LDL-C) has also been found to be an independent risk factor for the development of cardiovascular disease and is often reported to be the commonest lipid abnormality found in patients with DM [7, 8, 9]. The presence of elevated cholesterol levels is known to play a key role in both the initiation and progression of atherosclerosis, as well as in the clinical consequences such as myocardial infarction, stroke, peripheral vascular disease, and heart failure [10,11].Low levels of HDL-C have been consistently reported in cardiovascular diseases [12]. Although the triglycerides have been found to be univariate predictors of CVD in many studies, From the foregoing, it is evident that elevated cholesterol, low HDL-C, high TG and high LDL-C are all risk factors for CVD. [13,14].Metformin is an oral antidiabetic drug (biguanide class) [15]. It is used for the treatment of type 2 diabetes, in particular, overweight and obese people and those with

normal kidney function.[16] Its use in gestational diabetes, polycystic ovary syndrome. Metformin works by suppressing glucose production by the liver [17].Metformin is the only antidiabetic drug that has been conclusively shown to prevent the cardiovascular complications of diabetes [18]. It helps to reduce LDL-C and triglyceride levels, and is not associated with weight gain [19,20].Glyburide is an oral antidiabetic drug in the sulfonylurea's class used in the treatment of type 2 diabetes. Glyburide is a first line option for treating type 2 diabetes in people who are not overweight, or who cannot take metformin.[21] It is used when diet and exercise have failed to control blood glucose levels. It can also be used in combination with other antidiabetic medicines to provide better control of blood sugar [22]. Metformin and glyburide are widely used as oral antidiabetic drugs in Iraq, and many previous clinical and animal studies observed a possible lipid lowering role for them [23].

The aim of this study is to evaluate the effects of metformin, glyburide, and their combination on lipid profile through estimation of the level of Total cholesterol, LDL-C, HDL-C, TG-C. And VLDL-C. This study will provide information about the ability of these drugs in reducing atherosclerosis and hence reducing cardiovascular complications, frequently associated with type 2 DM in addition to their well known ability in lowering blood sugar[24]

Patients and Methods

1. Patients:

The subjects (patients and control) were studied at Al-Hindiya Hospital in Kerbala city, 148 individuals were included in this study aged from 39 – 58 years, weighted from 69 – 85 kg, 79 were men and 69 were women, all of them had NIDDM without other chronic disorder. Their blood sugar was under control within normal level according to treatment. None of them refused to participate. They were divided into 4 groups:-

Group A: 37 healthy age-matched individuals **(control group).**

Group B : 37 Type 2 diabetic patients on glyburide (10 mg / day) for 2 years **(Glyburide Group).**

Group C : 37 Type 2 diabetic patients on metformin (1000 mg / day) for 2 years **(Metformin Group).**

Group D : 37 Type 2 diabetic patients on combination therapy (metformin 500 mg / day + glyburide 5 mg / day) for 2 years **(Combination Group).**

2. Samples Collection:

Subjects fasted for at least 12-14 hours, after that the blood samples (5 ml) were collected on January 2011 between 8:00 and 10:00 am and serum was obtained after centrifugation at 3000 rpm for 10 minutes. The serum samples were stored at (-20 C^{o}) during the period of collection.

At the end of the period, serum samples were transferred to the Pharmacology Laboratory, at College of Medicine - University of Babylon where the biochemical analysis performed.

3. Biochemical Analysis:

3.1 Measurement of total cholesterol [25]

Total cholesterol was measured according to [25] using (Biomeriex) Kit.

3.2 Measurement of Triglycerides Concentration [26].

TG-C was measured according to [26] using (Biomerieux, France) kit.

3.2 Measurement of (HDL) Concentration [27].

HDL-C was measured according to [27] using (Biomerieux) Kit.

3.2 Measurement of (LDL and VLDL) Concentration [28].

LDL = Total cholesterol – (HDL + VLDL).

VLDL = Serum TG / 2.2.

Results

Serum TC levels were increased significantly in glyburide group (mean = 6.021 ± 0.430mmol/L) as compared with controls (mean ± SEM = 4.388 ± 0.467 mmol/L),. Metformin was found to keep serum **TC** at lower levels (mean ± SEM = 4.932 ± 0.614 mmol/L) than that observed with glyburide. In combination therapy serum TC level (mean = 4.414 ± 0.238 mmol/L) was lower than both glyburide and metformin used alone **Figure 1. , Table 1.** Regarding serum **TG**, there was clear elevation in their levels in diabetic patients taking glyburide (mean ± SEM = 2.459 ± 0.730 mmol/L) as compared with controls (mean ± SEM = 1.451 ± 0.367 mmol/L). In patients taking metformin, serum TG levels (1.567 ± 0.554) were lower than glyburide and with no any significant difference with controls. The use of combination therapy was shown to reduce the levels of serum **TG** (mean ± SEM = 1.562 ± 0.474 mmol / L) more than both glyburide and metformin used alone, **Figure 2. , Table 2.**Serum HDL was significantly decreased in glyburide (0.705 ± 0.222mmol) in comparison to control (1.161 ± 0.299mmol/L) group. Metformin (0.932 ± 0.602 mmol/L) and combination (1.110 ± 0.249 mmol/L) groups showed higher serum HDL level than glyburide group, **Figure 3. , Table 3.**Serum VLDL in glyburide (1.117 mmol/L) was significantly increase in comparison to control (0.659 mmol/L) group, while there was no significant difference between metformin (0.712 mmol/L) and combination (0.711mmol/L) groups compared with control group, **Figure 4. , Table 4.**Serum LDL level was significantly increase in glyburide (4.199 mmol/L) in comparison to control (2.568 mmol/L) group, while there was no significant difference between metformin (2.99 mmol/L) groups, combination (2.593 mmol/L) group and control group **Figure 5, Table 5.**

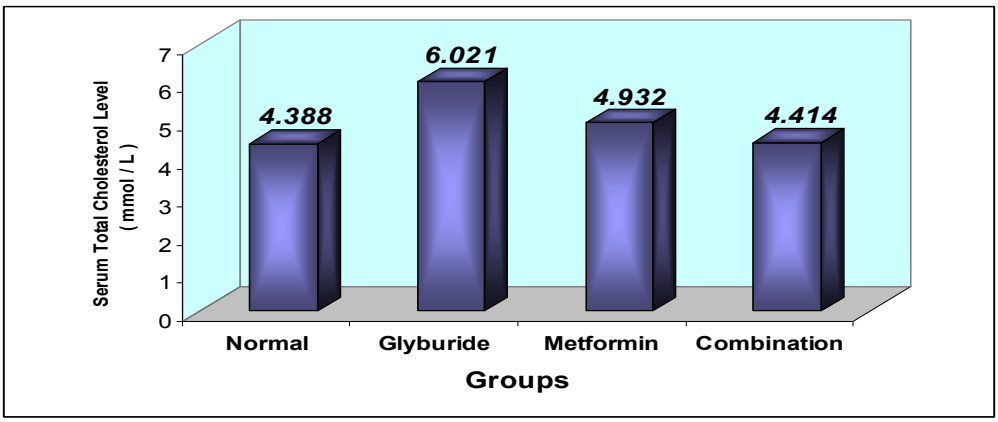

Figure (1):- Serum TC levels (mmol/L) in different groups.

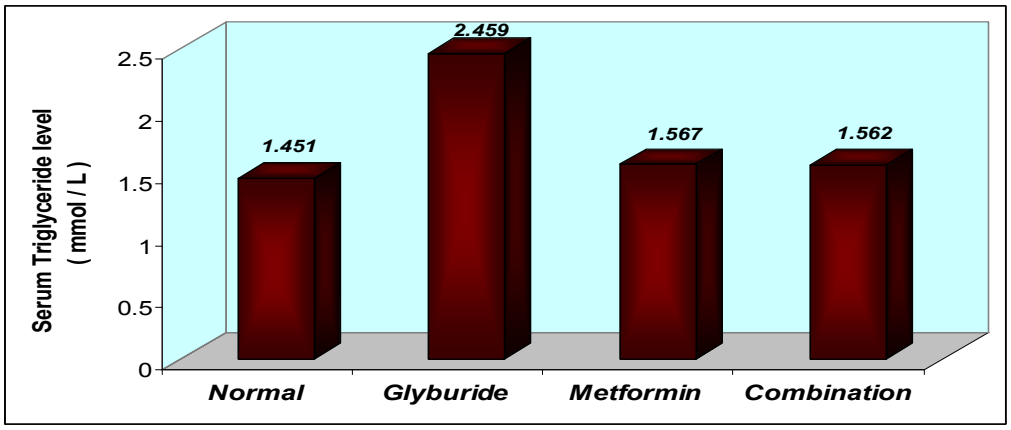

Figure (2):- Serum TG levels (mmol/L) in different groups.

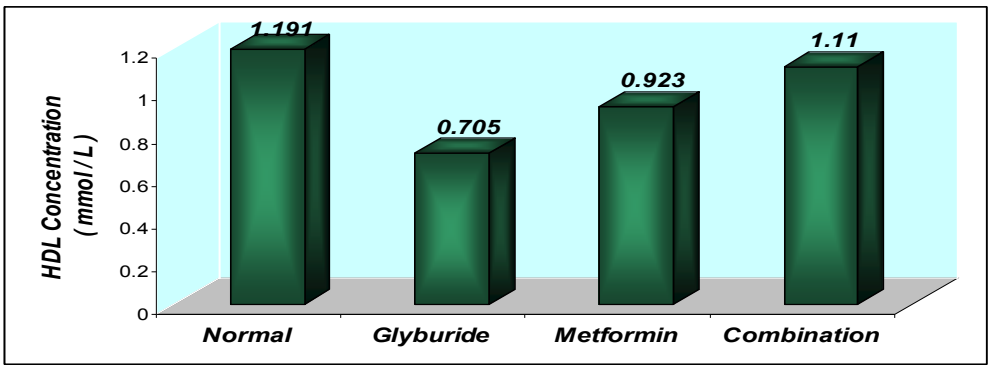

Figure (3):- Serum HDL levels (mmol/L) in different groups.

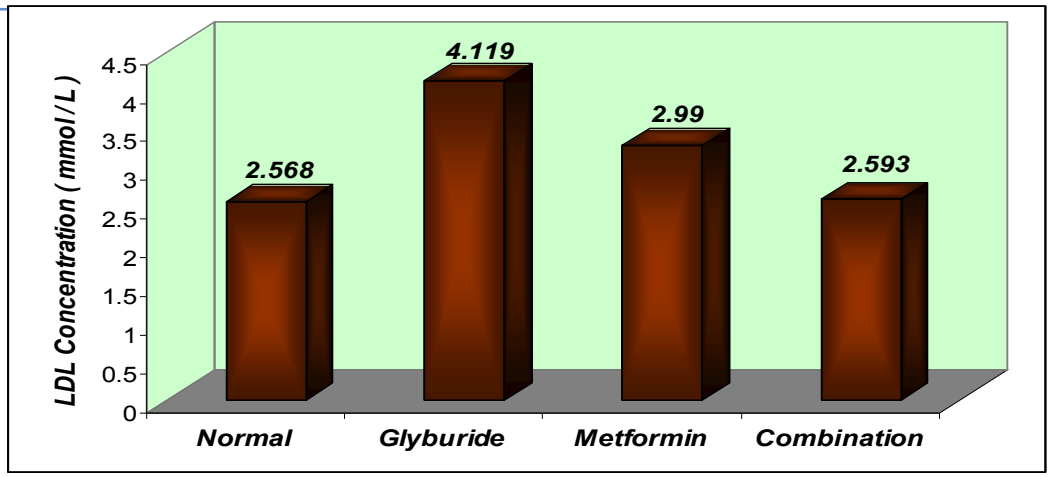

Figure (4):- Serum VLDL levels (mmol/L) in different groups.

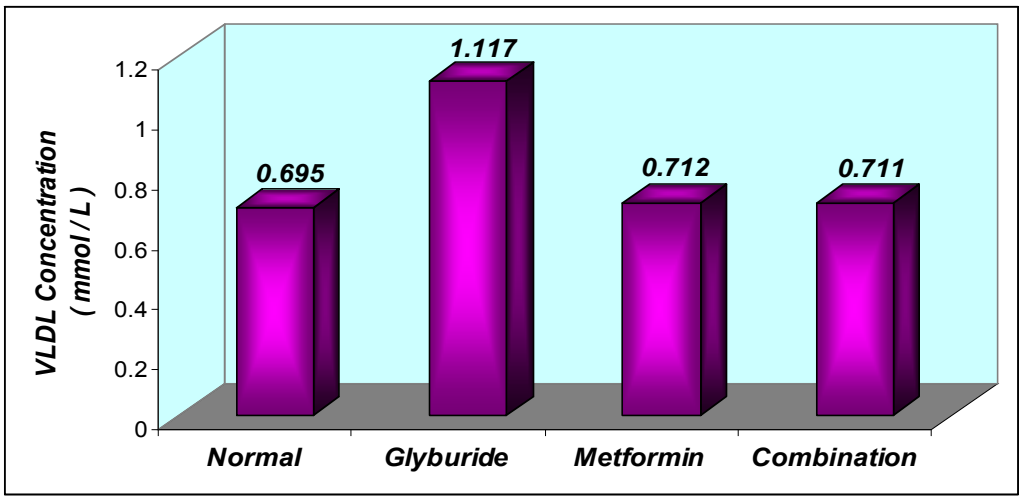

Figure (5):- Serum LDL levels (mmol/L) in different groups.

Table (1):- Comparisons between mean differences of serum TC levels (mmol/L) in different groups.

	Glyburide group	Metformin group	Combination group
Control group	1.633 ± 0.952 *	0.554 ±0.882	0.026 ±0.712
Combination group	1.607 ±0.701 *	0.525 ±0.619	
Metformin group	1.089 ±0.908 *		

Table (2):- Comparisons between mean differences of serum TG levels (mmol/L) in different groups.

	Glyburide group	Metformin group	Combination group
Control group	1.008 ± 0.377 *	0.116 ±0.371	0.111 ±0.409
Combination group	0.879 ±0.309 *	0.005 ±0.228	
Metformin group	0.892 ±0.701 *		

Table (3):- Comparisons between mean differences of serum HDL levels (mmol/L) in different groups.

	Glyburide group	Metformin group	Combination group
Control group	0.456 ± 0.388 *	0.229 ±0.601	0.051 ±0.411
Combination group	0.405 ±0.228 *	0.178 ±0.308	
Metformin group	0.281 ±0.409 *		

Table (4):- Comparisons between mean differences of serum VLDL levels (mmol/L) in different groups.

	Glyburide group	Metformin group	Combination group
Control group	0.458 *	0.053	0.052
Combination group	0.406 *	0.001	
Metformin group	0.405 *		

Table (5):- Comparisons between mean differences of serum LDL levels (mmol/L) in different groups

	Glyburide group	Metformin group	Combination group
Control group	1.631 *	0.129	0.025
Combination group	1.606 *	0.104 *	
Metformin group	0.902 *		

Discussion

In this study, there was clear hyperlipidemia present in glyburide group (group 2) in comparison with control group (group; *A*), metformin group (Group 3) and combination group (Group 4) .The same findings were observed by (Mohamad Ali Karimzadeh…et al) in a previous study [29]. This is clarified by increasing serum TC levels (Figure 1) (Table 1) ,increasing serum TG levels (Figure 2) (Table 2), decreasing serum HDL levels (Figure 3) (Table 3), increasing serum VLDL levels (Figure 4) (Table 4) and increasing serum LDL levels (Figure 5) (Table 5) in glyburide group as compared with controls, metformin and combination groups, while Metformin and combination groups was statistically not significant from controls, Santana et al (2004) have shown that treatment with metformin increased HDL level while serum total cholesterol and LDL levels reduced. [30].Motorman's beneficial effects on circulating lipids have been linked to reduced fatty liver. AMP-activated protein kinase (AMPK) is a major cellular regulator of lipid and glucose metabolism [31]. Here we report that metformin activates AMPK in hepatocytes; as a result, acetyl-CoA carboxylase (ACC) activity is reduced, fatty acid oxidation is induced, and expression of lipogenic enzymes is suppressed. Activation of AMPK by metformin or an adenosine analogue suppresses expression of SREBP-1, a key lipogenic transcription factor [32]. In Metformin-treated rats, hepatic expression of SREBP-1 (and other lipogenic) mRNAs and protein is reduced; activity of the AMPK target, ACC, is also reduced. Using a novel AMPK inhibitor, we find that AMPK activation is required for motormen's inhibitory effect on glucose production by hepatocytes [33].Regarding glyburide, many previous studies observed weak or insignificant lipid regulation properties when used as monotherapy [34]. Riddle MC.. et al, said that sulfonylureas alleviates the metabolic deviations in lipid and its peroxidation [35].

Conclusions

The use of metformin / glyburide combination or metformin alone in the treatment of NIDDM significantly maintained lipid profile at levels closer to that of non-diabetic controls.

- The use of combination therapy or metformin alone provide better protection against cardiovascular complications of DM and hence better prevention of complications like atherosclerosis than glyburide alone.

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