Effects of Oral Hypoglycemic Drugs on Serum Lipid Profile in Hyperlipidemic Rats

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Abstract

Background. Diabetes mellitus and hyperglycemia both are independent risk factors for coronary atherosclerosis, which is a major cause of death worldwide. The aim of this study is to elucidate the effects of some hypoglycemic drugs on serum lipid profile in hyperlipidemic, non- hyperglycemic rats, and to see whether these effects are related to their hypoglycemic effects.

Materials and Methods: This study included 50 rats which have been randomly allocated into five groups, 10 for each group. One of these groups was put on normal diet, and considered as a control group, the remaining four groups were feed with fat-rich diet for eight weeks.

Before starting treatment with hypoglycemic drugs, blood samples were collected form these five groups, and serum lipid profile namely, triglycerides(TG), total cholesterol (TC), low density lipoprotein (LDL), very low density lipoproteins(VLDL), and high density lipoproteins (HDL), were measured. The results have revealed that the four groups have become hyperlipidemic. Then one group out of the four hyperlipidemic groups received distilled water, while the other three received one of the following hyperglycemic drugs: Metformin, Rosiglitazone, and Acarbose. The four groups were kept on fat-rich diet four eight weeks.

Results: 1). All three hypoglycemic agents produced a highly significant reduction in the level of TG compared to control. However, the magnitudes of reduction varied from one drug to another. 2). Metformin and Rosiglitazon produced a significant reduction in the level of total serum cholesterol (TC) compared to control . Acarbose produced non-significant reduction in the level of TC compared to control. 3). Metformin produced a highly significant reduction in the level of LDL , Rosiglitazone produced reduction in the level of LDL, however this reduction is not significant. Acarbose, on the other hand, produced a highly significant increase in the level of LDL. 4). Metformin, Rosiglitasone, and Acarbose all produced a highly significant reduction in the level of VLDL . 5). Metformin produced a highly significant increase in the level of HDL ($P<0.01$), while Rosiglitazone and Acarbose produced a significant reduction in the level of HDL ($P<0.05$).

Conclusions: Metformin reduced serum levels of Triglycerides TG, total serum cholesterol TC, low density lipoprotein LDL, and very low density lipoprotein VLDL, but increases serum level of high density lipoprotein HDL. These effects may share in decreasing the risk of atherosclerosis. Rosiglitazone reduces serum TG, TC, VLDL, and HDL levels, but has no effect on serum LDL level. Rosiglitazone therefore, should be cautiously prescribed for patients with cardiac problems. Acarbose reduces serum TG, VLDL, HDL, and increases LDL levels, but has no effect on TC. Acarbose should also be used cautiously in patient with cardiac problems.

تأثير خافضات السكر الفموية على مستويات الدهون في مصل الدم عند الجرذان

الخلاصة

خلفية البحث: يعتبر دائي السكري وارتفاع مستويات الدهون في الدم عاملي خطورة مستقلين لآفة التصلب العصيدي في الشرايين الاكليلية القلبية، و التي تعتبر القاتل الاول على المستوى العالمي. لقد اظهرت الدراسات والبحوث التي اجريت على داء السكري، انه من عوامل الخطورة التي تساعد في نشوء افة العصيدة الشريانية، وان السبب في ذلك يعود الى ان داء السكري غالبا ما يكون مصحوبا باضطراب مستويات الشحوم بالدم.اظهرت الدراسات والوبائية ان علاج داء السكري قد ساهم كثيرا في الحد من نشوء افة التصلب الشرياني. ان الهدف من هذا البحث هو دراسة تاثير بعض خافضات السكر الفموية على مستوى الدهون في مصل الدم، واي منها اكثر تأثيرا.

المواد وطريقة العمل:استخدمنا في هذا البحث خمسين جرذا من فصيلة (سبرانكو دوايلي) حيث قسمت هذه الحيوانات عشوائيا الى خمسة مجاميع: المجموعة الاول اعطيت غذءا قياسيا لمدة ١٦ اسبوعا واعتبرت كمجموعة سيطرة طبيعية. المجاميع الاربعة الاخرى اعطيت غذاءا عالي الدسم لمدة ٨ اسابيع. بعدها اخذنا عينات من دمها لقياس مستوى الدهون وهي الكلسيريدات الثلاثية، الكوليسترول الكلي، الكوليسترول واطيء الكثافة، الكوليسترول جدً واطيء الكثافة، والكوليسترول عالي الكثافة، و بعد ان اصبحت جميع الحيوانات عالية دهن الدم اعطينا احداها ماءً مقطرا واعتبرت مجموعة سيطرة عالية الدهن، اما المجاميع الثلاث الاخرى فقد اعطي كل واحد منها واحدا من الادوية الخافضة للسكر التي تضمنتها الدراسة وهي: الميتفورمين، الروزكليتازون، و الاكربوز.

النتائج: ١) جميع الادوية الثلاث التي استعملت في هذه الدراسة احدثت انخفاضا ذا قيمة معنوية عالية في مستوى الكلسريدات الثلاثية في الدم. ٢) احدث كل من عقاري الميتفورمين و الروزكليتازون انخفضا ذا قيمة معنوية في مستوى الكوليسترول الكلي في الدم، بينما لم يحدث عقار الاكربوز انخفاضا ذا قيمة معنوية فيه. ٣) احدث عقار الميتفورمين انخفاضا ذا قيمة معنوية عالية في مستوى الكوليسترول واطيء الكثافة، بينما لم يسبب عقار الروزكليتازون نقصانا معنويا فيه، في حين، احدث عقار الاكربوز زيادة في مستوى الكوليسترول واطيء الكثافة. ٤) الادوية الثلاث احدثت انخفاضا ذا قيمة معنوية في مستوى الكوليسترول جد واطيء الكثافة مع فوارق متباينة . ٥.) احدث عقار الميتفورمين زيادة معنوية في مستوى الكوليسترول عالي الكثافة بينما احدث الروزكليتازون و الاكربوز نقصانا معنويا في مستواه.

الاستنتاج : احدثت الادوية الثلاث التي استعملناها تأثيرات متفاوتة على مستويات الدهون في الدم. كان اكثرها فائدة من ناحية التقليل من مخاطرالتصلب الشرياني هو الميتفورمين. كل الادوية الثلاث احدثت نقصانا معنويا في مستوى الكلسريدات الثلاثية، وهي بذلك تصبح ذات فائدة اذا كان ارتفاع مستوى دهون الدم سببه زيادة مستوى الكلسريدات الثلاثية. علينا توخي الحذر في استعمال الروزكليتازون والاكربوز في الاشخاص الذين يعانون من ارتفاع الدهون الناتج عن ارتفاع مستوى الكوليسترول واطيء الكثافة.

Introduction

Serum lipids are present in two forms, triglycerides and cholesterol that are incorporated within the lipoproteins which act as a vehicle for their transport [1]. According to their molecular weight and their contents of lipids and protein, lipoproteins are classified into four categories; a) chylomicrons, b) VLDL, which are the least dense and contains a core composed primarily of triglycerides, c) LDL, and d) HDL [2]. The last two members are the densest and contain a core that is composed primarily of cholesterol.

Lipoproteins act as an efficient vehicle for site to site transport of TG and exogenous and endogenous cholesterol. Lipoprotein allows the excess of calories that enter the circulation with each meal to be transported as TG and to be stored in the adipose tissue for future utilization between meals to supply free fatty acids. TG-rich lipoproteins can enter plasma as chylomicrons derived from the dietary fat absorbed from the gut, or as TG-rich VLDL synthesized in the liver from glucose and free fatty acids [3].

Dietary TG is carried in blood stream on chylomicrons. These chylomicrons become progressively smaller as a result of continuous lipolysis that takes place at the capillary endothelium of adipose tissue, skeletal muscles, and cardiac muscles by the action of lipoprotein lipase enzymes. The free fatty acids liberated during lipolysis are taken up by tissue and the chylomicrons remnants are cleared by the liver [3]. Endogenous triglycerides are synthesized by the liver from glucose and free fatty acids and carried in the blood bound to VLDL. Then, VLDL is progressively removed from the circulation by the same manner as chylomicrons [4].

LDL constitutes the major system for delivery of cholesterol to the tissue in man. Synthesized in liver, LDL molecule is small enough to pass through the vascular endothelium by binding to specific high-affinity LDL receptors on cell membrane, so that

LDL enter the cell by active uptake mechanism [5]. HDL, the other cholesterol-rich lipoprotein in the blood, appears to act as reverse transport mediator that accepts cholesterol from peripheral cells, for example from the arterial endothelial cells, to the liver [6]. Thus, HDL acts as scavenger for cholesterol and by this virtue it has a protective effect against atherosclerosis [7].

Dyslipidemias is probably a better term to describe changes in serum lipid profile, including all lipid and lipoprotein abnormalities such as low level of HDL [8]. Dyslipidemias can be classified into primary and secondary dyslipidemias, depending on the causes. Primary types are due to genetic defects, especially in genes responsible for production of LDL receptor. Secondary hyperlipidemias are associated with other diseases such as diabetes mellitus, hypothyroidism, nephritic syndrome, and obstructive lung diseases [9].

Dyslipidemia is a common finding in diabetes mellitus because both insulin deficiency and insulin resistance affect the enzymes and metabolic pathways of lipid [10]. Therefore, diabetes mellitus constitutes a major risk factor for development of atherosclerosis and ischemic heart diseases. The prevalence of dyslipidemia in type II diabetes mellitus may vary between different ethnic groups. It has been suggested that genetic and environmental factors, as well as the duration and severity of the diabetic state, may play a role in influencing lipid level [11]. Both hypertriglyceridemia and hypercholesterolemia have been reported among adult diabetic individual [11]. Since both insulin deficiency and insulin resistance affect the enzymes and metabolic pathways of lipid metabolism, resulting in hyperlipidemia, it seem to be logical to infer that hypoglycemic drugs may have some effects on serum lipid profile.

The aim of the present study is to reevaluate the effects of some new generation of hypoglycemic drugs on serum lipid profile in hyperlipidemic, non-hyperglycemic rats treated with these drugs.

Materials and Methods

1. Preparation of Experimental Animals: The study was conducted in year 2001, on 50 male Spraguilo-Dawely rats supplied by the National Center for Drug Control and Research (NCDR) in Baghdad. The animals were housed in Al-Kufa Medical College's animal house. The animals were exposed to controlled temperature around 25c and artificial 12 hours light-dark cycles. The animals were left under these situations without interference for acclimatization for 2weeks. After that period 10 rats were put on normal chow diet for 16 weeks and considered as control group and designated as (group1). The remaining forty rats were put on cholesterol-rich diet which was made by addition of 4% cholesterol powder to the standard chow diet.

After 8 weeks of this dietary regimen, blood samples were collected and analyzed for serum lipids components. All the forty rats fed with cholesterol-rich diet have become hyperlipidemic as compared with control group. Then, the forty hyperlipidemic rats were subdivided into four groups, each group contains ten rats. The first group (group II) received distilled water, and the other three groups (group III, Group IV, and group V) received one of the three used hypoglycemic drugs (Metformin, Rosiglitazone, and Acarbose) as follow: group III received Metformins, group IV received Rosiglitazone, and group V received Acarbose. The treatment with

hypoglycemic drugs was continued together with cholesterol-rich diet for another 8 weeks.

2. Preparation of Drugs. We chose three of the most commonly used hypoglycemic drugs, namely Metformin, Rosiglitazone, and Acarbose.

Metformine: A 500 mg tablets "glucophage" supplied from Lipha Sante: Batch no. 1991 and a dose of 30 mg/kg have been used (12). The dose was calculated according to body weight for each animal in group III, dissolved in 5cc of distilled water and administered in daily regimen through a stomach tube for eight weeks.

Rosiglitazone: A 4 mg tablet "Avandia" supplied from Smith Kline Beecham Pharmaceutical: Batch no. N20212A.5g. a dose of 2mg/kg had been used (13). The drug was dissolved in 4 cc distilled water and the dose was calculated according to body eight for each member of group IV and administered on daily regimen through stomach tube for eight week.

Acarbose: A 100 mg tablet "glucobay" supplied from Bayer, Batch no. CBKTL3.A., a dose of 50mg/kg was used (14). The drug was dissolved in 5cc DW and the dose was calculated according to body weight for each animal in group V and administered on daily regimen through stomach tube for eight weeks.

3. Collection of Blood Samples: After overnight fasting, 1ml of blood was withdrawn from the caudal artery of each animal. The blood was left for half an hour to stand, and then centrifuged at 3000 RPM for 15 minutes. 0.6 ml of the serum was obtained and immediately analyzed by micro-photo-meter.

The measurement for TG was done at wave length 505nm, for total cholesterol at wave length 500nm, and for HDL at wave length 500nm (15). The measurements for VLDL and LDL are based on the equations: VLDL =TG/5, and LDL= total cholesterol – HDL+VLDL.

4. Statistical Analysis. The data obtained were expressed as mean – SEM unless otherwise stated and expressed as mg/dl, ANOVA. The pair wise comparisons have been used and the significance was accepted at P=0.05.

Results

After 8 weeks, all animals which have been fed with cholesterol-rich diet become hyperlipidemic when compared with animals that have been kept on normal chew diet. The hyperlipidemia involved the main plasma lipid component, namely triglycerides TG, total serum cholesterol TC, VLDL, LDL, and HDL, table 1.

Table 1 Mean values of serum lipid profile in normal control rats and rats which have been fed with cholesterol-rich diet after 8 weeks; values are expressed as mg/dl

Lipid component	Normal control	Cholesterol fed after 8 weeks	P. Value
Triglycerides	112. 05 + 1.61	170.02 + 1.02	<0.05
Total Cholesterol	111. 15 +0.71	163.39 + 1.12	<0.05
LDL	58.70 +1.35	89.61 +1.09	<0.05
VLDL	22.41 +0.89	34.05 +0.20	<0.05
HDL	30.04 + 0.67	39.82 +0.38	<0.05

Values are expressed as mean + SEM

Effects on triglycerides: After 8 weeks of treatment with a hypoglycemic agent, all animals in the study groups show a highly significant reduction in serum triglycerides levels in comparison to hyperlipidemic control group (P<0.01). The lowest values of reduction are observed in rosiglitazone-treated group, while the highest values of reduction are seen in acarbose-treated-group, table 2 and 3.

Table 2 Mean values of the percentage of change from the base line in serum triglycerides after treatment with hypoglycemic drugs compared to the untreated hyperglycemic control.

Groups	**Serum Level of TG before treatment**	**Serum level of TG after treatment**	**% of change from the base line**
Group II Untreated Control	170.02 +1.02	200.51+ 1.90	17%
Group III Metformine	180.57 +0.34	182.37 + 1.01	0.9%
Group IV Rosiglitazone	179.49 +0.40	182.22 + 0.98	1.5%
Group V Acarbose	179.68 +0.57	177.05 + 1.12	-1.5%

Table 3 LSD multiple comparisons between treated groups for TG values

	X = 182.37 Metformin	**X = 182.22 Rosiglitazone**	**X = 177.05 Acarbose**
X = 200.51 Hyperlipidemic control	** 18.14	** 18.29	** 23.46
X = 177.05 Acarbose	* - 5.32	- 5.17	
X= 182.22 Rosiglitazone	- 0.51		

** P< 0.01 highly significant, * P< 0.05 significant.

Effects on total serum cholesterol: Metformin-treated group shows a highly significant reduction in the levels of TC (P<0.01). A significant lowering effect is also observed in animals treated with rosiglitazone (P<0.05). Acarbose-treated animals show non-significant reduction in TC level compared to control (P>0.05). Tables 4 and 5.

Table 4 Mean values of the percentage of change from the base line in total serum cholesterol after treatment.

Group	**Before treatment**	**After treatment**	**% of change from the base line**
Group II	163.39 + 1.12	191.30 +0.93	17
Group III	164.12 +1.43	175.70 + 0.66	7
Group IV	159.60 + 1.40	178.57+0.75	11
Group V	158. 28 +0.99	184.08 + 1.37	١٦

Table 5 LSD Multiple comparisons between treated groups for TC.

	X= 175.70 Metrormin	**X=178.57 Rosiglitazone**	**X=184.08 Acarbose**
X = 191.30 Hyperlipidemic control	** 15.60	** 12.73	** 7.22
X= 184.08 Acarbose	** 8.38	** 5.5	
X = 178.57 Rosglitazone	2.87		

** P< 0.01 highly significant

Effects on LDL-cholesterol: The three hypoglycemic drugs showed different patterns of effect on LDL-cholesterol levels; metformin causes a highly significant reduction (P<0.01) in the level of LDL. Rosiglitazone shows no significant reduction in the level of serum LDL when compared to control P>0.05). Acarbose shows a highly significant increase in the serum levels of LDL (P<0.01), tables 6 and 7.

Table 6 Mean values of the percentage of change from the base line in serum LDL.

Group	**Before treatment**	**After treatment**	**% of increase**
Group II	89.61+ 1.09	110.08 +1.15	22
Group III	84.19+ 1.41	91.75 + 0.49	10
Group IV	82.64 + 1.19	101.44 + 0.56	22
Group V	81. 77 + 0.82	108.52 + 1.06	32

Table 7 LSD multiple comparisons between treated groups for LDL values

	X=91.75 metformin	**X=101.44 Rosiglitazone**	**X=108.52 Acarbose**
X=110.08 Hyperlipidemic control	** 18.33	** 8.64	** 1.56
X= 108.52 Acarbose	** 16.77	** 7.08	
X =101.44 Rosiglitazone	** 9.69		

Effects on VLDL: All treated groups show a highly significant reduction in serum VLDL level (P<0.01)in comparison to control group. Acarbose causes the highest level of reduction, while rosiglitazone causes the lowest reduction in VLDL level, tables 8 and 9.

Table 8 Mean values of change from the base line in serum VLDL after treatment.

Group	Before treatment	After treatment	% of increase
II	34.05 +0.20	40.10 + 0.38	17
III	36.11 + 6.83	36. 48 +0.20	1.5
IV	35.80 +8.67	36.44 + 0.19	1.7
V	35.98 +0.10	35. 41+ 0.22	-1.5

Table 9 LSD multiple comparison of mean values of serum VLDL between treated groups.

	X =36.48 Metfromine	X =36.44 Rosiglitazone	X = 35.41 Acarbose
X= 40.10 hyperlipidemic control	** 3.62	** 3.66	** 4.69
X =35.41 Acarbose	* -1.07	* -1.03	
X=36.44 Rosiglitazone	* -0.04		

**** P<0.01. * P<0.05.**

Effects on HDL: Metformin produces a highly significant increase in serum HDL level in comparison to control group (P<0.01). Both, rosiglitazone and acarbose produce a significant reduction in serum HDL levels (P<0.01), tables 10 and 11.

Table 10 Mean values of the percentage of change from the base line in serum HDL after treatment

Group	Before treatment	After treatment	% of increase
II	39.82 + 0.38	41.12 +0.79	3.2
III	43. 82 + 0.52	47.48 + 0.55	8.3
IV	41.07 +0.61	40.72 +0.55	-0.8
V	40.53+ 0.37	41.05 + 0.73	1.2

Table 11 LSD Multiple comparison of the mean values of serum HDL between treated groups.

	X=47.48 Metformin	X= 40.72 Rosiglitazone	X=41.05 Acarbose
X=42.12 hyperlipidemic control	** -6.36	0.40	0.07
X =41.05 Acarbose	** -6.43	0.33	
X= 40.72 Rosiglitazone	** -6.76		

****** P< 0.01 highly significant.

Discussion

Oral Hypoglycemic comprise a group of drugs that are capable of lowering blood sugar level by different mechanisms including improvement of insulin secretion such as sulphonylurease and repaglinide [16], improvement of insulin action on the liver and muscles such as metformine [17], improvement of insulin action on the muscle and fat like thiazolidinediones [18], and slowing the digestion and absorption of carbohydrate available in meals like acarbose [19].

Effects on Serum Lipids

Dyslipidemia, including decreased plasma HDL cholesterol levels, is usually present in those with poorly controlled type 2 diabetes [20- 22]. As these abnormalities are now recognized to be major contributors to the development of arterial vascular disease, there is significant interest in the beneficial effects of antidiabetic agents, particularly those that reduce insulin resistance, such as metformin [10] and troglitazone [18], on lipid metabolism.

Effects of Metformine: Our study has shown that metformin therapy has been associated with significant decrease in plasma triglycerides, total plasma cholesterol TC, LDL-cholesterol, and VLDL- cholesterol, and significant increase in plasma HDL- cholesterol. These findings are in agreement with other studies [23-26]. However, some studies have demonstrated small increases [27], or only small decreases [28, 29] in total plasma cholesterol, LDL, and triglycerides.

The hypoglycemic effect of metformin occurs via inhibition of release of fatty acids from central adipose tissues [10]. Visceral fat seems to be metabolically unique in that it results in hepatic insulin resistance by increasing the influx of free fatty acids from the omental fat into the liver. Increased influx of free fatty acids into the liver results in increased hepatic glucose production HGP and hepatic insulin clearance, which in turn lead to insulin resistance and hyperinsulinemia [20,30].

The association between insulin resistance and obesity has been well established [20, 21]. It has been shown that surgical removal of visceral fat in obese rats reversed insulin resistance [30], it has also been observed that loss of visceral fat by aging resulted in improvement of hepatic sensitivity to insulin [31]. The most common pattern of dyslipidemia in type II DM patients are hypertriglyceridemia and decreased level of HDL [32]. Therefore, metformine is a useful treatment in diabetic patients who suffer from hypertriglyecidemia. This antihyperlipidemic effect of metformin is due to inhibition of fatty acids release from adipose tissues [33].

Reductions in plasma total cholesterol levels appear to be the result of decreased levels of LDL or VLDL cholesterol. It has been suggested that the effect of metformin on lipids is independent of its antihyperglycemic effect [34]. Although the exact mechanism by which these lipid changes occur has not been determined, they may occur as a result of a direct effect of metformin on VLDL cholesterol metabolism and/or secondarily to improved insulin sensitivity.

Effects of Rosiglitazone

Rosiglitazone is a member of a group of hypoglycemic drugs called thiazolidinediones. Thiazolidinediones are insulin sensitizing agents that act primarily by enhancing peripheral glucose utilization. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferators–activated receptor gamma (PPARγ). In humans, PPAR receptors are found in key target tissues for insulin action such as

adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPARγ-responsive genes also participate in the regulation of fatty acid metabolism [35, 36].

Our study shows that rosiglitazone therapy has been associated with a highly significant reduction in total plasma cholesterol and VLDL, and this agree with the results obtained by Neelma et al, [25]. This effect may be due to improved insulin sensitivity [31]. Rosiglitazone significantly reduces serum total cholesterol P< 0.01, however, Neelma did not find the same results. This reduction in the level of total serum cholestrole in our study seem to be mainly due to reduction in the level of VLD and HDL, because the result of our study shows that rosiglitazone has no effect on plasma LDL and significantly reduced plasma HDL. Other studies have shown that Rosiglitazone induces increases from baseline in both LDL cholesterol (by 5–15%) and total cholesterol (by 1–8%) [35, 36]. In two placebo-controlled studies, the increase in LDL cholesterol was significant (P < 0.05), compared with the change seen with placebo [35, 36]. The differences between our results and these studies may be attributed to the duration of treatment. Our study has also demonstrated that rosiglitazone therapy has been associated with a highly significant reduction in plasma triglycerides. Other studies has shown that Troglitazone reduces serum triglyceride levels, but in two monotherapy studies, only the 600 mg/day dosage produced significant reductions (P < 0.05) compared with placebo [35].

Effects of Acarbose:

Acarbose inhibits enzymes (glycoside hydrolases) needed to digest carbohydrates: specifically alpha-glucosidase enzymes in the brush border of the small intestines and pancreatic alpha-amylase. Pancreatic alpha-amylase hydrolyzes complex starches to oligosaccharides in the lumen of the small intestine, whereas the membrane-bound intestinal alpha-glycosidase hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine. Inhibition of these enzyme systems reduces the rate of digestion of complex carbohydrates. Less glucose is absorbed because the carbohydrates are not broken down into glucose molecules [19].

Our study shows that acarbose therapy has been associated with a highly significant reduction in the level of serum triglycerides (p<0.01), the same results have been shown in other studies [37- 39]. However, there is no significant reduction in total serum cholesterol (P> 0.05). Some studies have shown that Acarbose reduces serum triglyceride concentrations but has little or no effect on total serum cholesterol concentrations [40]. This effect appears to be mediated by suppressing the biosynthesis of VLDL cholesterol [40]. A review of more recent studies reported that fasting triglyceride levels are reduced, but only occasionally(20). This effect appears to be associated with dosages >100 mg three times a day [37-39]. Of the studies that used dosages <300 mg/day, none demonstrated statistically significant changes, relative to baseline or placebo, in fasting triglyceride, total cholesterol, or cholesterol fractions [41].

Conclusion

Metformin reduces serum levels of TG, TC, LDL, VLDL, and increases serum level of HDL. These effects may share in decreasing the risk of atherosclerosis.

Rosiglitazone reduces serum TG, TC, VLDL, and HDL levels, but has no effect on serum LDL level.

Acarbose reduces serum TG, VLDL, HDL, and increases LDL levels, but has no effect on TC.

Recommendations

1. Metformin seems to be the best hypoglycemic drug to start with in patients whose medical histories, regarding cardiac problems, are not clear.
2. Rosiglitazone and Acarbose should cautiously be given to patient with ischemic heart diseases, because they deprive the body from the beneficial anti-hyperlipidemic effect of HDL.
3. The effects of Rosiglitazone and Acarbose on triglycerides are superior to those of Metformin, and therefore these two hypoglycemic agents may be preferred for metformin in patients who have no cardiac problems and whose hyperlipidemia is mainly due to hypertriglyceridemia.

References

1. Haq IU, et al: Sheffield risk and treatment table for cholesterol lowering for primary prevention of coronary heart diseases. *Lancet 346:1467-1471, 1995.*
2. Dietschy JM and Wilson JD: Regulation of cholesterol metabolism. *N Engl. J med 282: 1128-38, 1970.*
3. Louis J, Elasas II: Metabolic diseases. *In Cecil textbook of Medicine PP: 1093-1094, 21st. Edition, 2000.*
4. Brunzell, Austin MA: Plasma triglycerides level and coronary diseases. *N Engl. J. Med 320: 1273, 1989.*
5. Rum Mac Sween and Chuhaley: Diseases of Cardiovascular system. *In Muir's textbook of Pathology PP: 449-450, 13th edition, 1992.*
6. Beteridge DJ: High density lipoprotein and coronary heart diseases. *BMJ 289: 974, 1989.*
7. Journal of lipid diseases 25: 1425-1436, 1984.
8. Goldman and Bennet: Epidemiology of cardiovascular diseases. *In Cecil Textbook of Medicine PP: 167-168, 21st edition, 1987.*
9. Ginsberg HN and Goldbery JJ: Disorders of intermediary metabolism. *In Harrison Textbook of Medicine PP: 2138-2148, 8th edition, 1996.*
10. Unsitup M, Sutanen O, Vantilalnen E, et al: Serum lipids and lipoproteins in newly diagnosed non-insulin dependent diabetic patients, with special reference to HDL and triglycerides. *Diabetes Care 9: 17-22, 1986.*
11. Despres JP: Abdominal obesity as important component of insulin resistance syndrome. *Nutrition 9: 452-459, 1993.*
12. Anurage P, Anuradha CV: Metformin improves lipid metabolism and attenuates lipid peroxidation in high- fructose fed rats. *Diabetes- Obs-Metab 4(1): 36-42, 2002.*
13. Jiang Z, Li F, Lin M, Win D: Potentiation of insulin signaling in tissue of Zucker obese rats after acute and long-term treatment with PPAR-y agonist. *Diabetes 51: 2412-1419, 2002.*
14. Yamamato M, et al: Metabolic abnormalities in genetically obese and diabetic fatty rats can be prevented and reversed by a-glucosidase inhibitors. *Metabolism 48(3): 347-54, 1999.*
15. Assmann G: Internist 20: 559, 1979.
16. Klien R, et al: The medical management of hyperglycemia over 10

years in people with diabetes. *Diabetes Care 19:744-52, 1996.*
17. Slesnolfi-Baezl: Characterization and significance of sulphonylurea receptors. *Diabetes Care 3 (suppl): 2-8, 1990.*
18. Defronzo RA, Pharmacologic therapy for type 2 diabetes mellitus. *ANN. Inter. Med. 131:281-303, 1999.*
19. Fischer s, HanfieldM, Spengler M, Boehme K: European study on dose-response relationship of acarbose as first line drug in NIDDM, efficacy and safety of low and high dose. *Acta. Diabetol. 35: 34-40, 1998.*
20. Gibbons GF, Hyperlipidemia of diabetes mellitus. *Clin. Sc. 71:477-486, 1988.*
21. Tylor SI, Aaccili D, Lmais Y, Insulin resistance or insulin deficiency, which is the primary cause of NIDDM. *Diabetes 93: 735-740, 1994.*
22. Defronzo RA, Ferrannini E: Insulin resistance, a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerosis. Cardiovascular diseases, *Diabetes Care 14: 178-194, 1991.*
23. Giugliano, Marefll R, and Acrmpora R, Buoninconti R: Metformin improves glucose, lipid metabolism, and reduces blood pressure in hypertensive obese women. *Diabetes Care 10:1387-1390, 1993.*
24. Chen CC, et al: Comparison of the metabolic effects of metformin and trogletazone on fructose induced insulin resistance in male Spragne Dawley rats. *J. Fromos. Med. Assoc. 100(3): 176-180, 2001.*
25. Neelima V, Alice PS, Deniss D, et al: Differential effects of metfoemin and troglitazone on cardiovascular risk factors in patients with type 2 DM. *Diabetes Care 25: 542-549, 2002.*
26. Defronzo R, Goodman A, The multicenter study group: Efficacy of metformin in patients with NIDDM. *N Engl. J. Med. 33: 541 549, 1995.*
27. Hermann LS, et al: Therapeutic comparison of metformin and sulphonylurea alon and in various combinations. *Diabetes Care 17:1100-1109, 1994.*
28. Hoether-Nielson, et al: Metformin improves peripheral but not hepatic insulin action in obese patients with type 2 Dm. *Acta Endocrinologica (Copenhagen) 120: 257-265, 1989.*
29. Rains SGH, Wilson GA, Richmond W, and Eikeles RS: Effects of Glibenclamide and metformin on serum lipoprotein in type 2 diabetes mellitus. *Diabetic Med. 5: 653-658, 1988.*
30. Martha L, Cruz, et al: Unique effect of visceral fat on insulin sensitivity in obese Hspanic children with family history of type 2 diabetes mellitus. *Diabetes Care 25: 1631-1636, 2002.*
31. Bjorntor PP: Portal adipose tissue as generator of risk factors for cardiovascular disease and diabetes mellitus.
32. Turner RC, et al: Risk factors for coronary artery disease in NIDDM. *BMJ 316: 823-828, 1998.*
33. Abbasi F, Kamath V, et al: Results of placebo-controlled of the metabolic effects of the addition of metformin to sulphonylurea treated patients, evaluation of the central role of adipose tissue. *Diabetes Care 20:1863-1869, 1997.*
34. Sirtori CR, Lovati MR, Biguanids in hypertriglyceremia and the management of arterial diseases. In atherosclerosis Review: *Gotto AM Jr. Paoletti R. Eds New York, Raven Press, 1991, P. 155-162.*
35. Kumar S, Boulton AJM, et al: Troglitazone, an insulin action enhancer, improves metabolic control in NIDDM patients. *Diabetologia 39: 701-709, 1996.*
36. Valiquett T, Huang S, Whitcomb R: Effects of troglitazone monotherapy in patients with NIDDM: A 6 month

multicenter study. *Abstract. Diabetes 16(supple): 43 a, 1997.*
37. Akazawa Y,: Clinical usefulness of acarbose and fibers in the treatment of diabetes mellitus. *Therapeutics 36: 848-849, 1982.*
38. Jean L, Robert GJ, et al: The efficacy of acarbose in the treatment of patients with NIDDM. *Ann. Inter. Med. 121: 928-935, 1994.*
39. Lardinois CK, Greenfield MS, et al: Acarbose treatment of NIDDM. *Arch. Inter. Med. 144:345-347, 1984.*
40. Clissold SP. Edwards C, Acarbose: A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potentials. *Drugs 35: 241-243, 1988.*
41. Hanefield M, Fischer S, et al: Therapeutic potentials of acarbose as first-line drug in NIDDM insufficiently treated with diet alone. *Diabetes Care 14: 732-737, 1991.*