Review Article

Lipid Lowering Effect of Anti Diabetic Agents-Recent Research

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ABSTRACT

Diabetes mellitus type 2(T2DM) is a multifactorial metabolic disease characterized by abnormalities at multiple organ sites. In T2DM, the disturbances in lipid profiles, especially increased susceptibility to lipid peroxidation leads to atherosclerosis due to increased oxidation of low-density lipoproteins (LDL) and impaired vascular function. In patients with T2DM, besides controlling blood pressure and lipid levels, the major therapeutic goal is to optimize glycaemic control in order to reduce the development and severity of long-term diabetic complications. U.K. Prospective Diabetes Study (UKPDS) emphasize life-style management, diet, and exercise as the first-line approach, followed by therapy with hypoglycemic or antihyperglycemic agents, either alone or in combination. Type 2 diabetes and elevated plasma lipid levels are important independent risk factors for cardiovascular disease like coronary heart disease. The choice of an antihyperglycemic agent for patients with type 2 diabetes in whom abnormal plasma lipid levels are often seen should take into account for effective lipid control. Patients with type 2 diabetes are at 2 to 4 fold greater risk for coronary heart disease and stroke and 2 to 8 fold greater risk for heart failure than the general population. Recent prospective and retrospective studies have confirmed that the antidiabetic drugs have favourable effects on lipid profile. Given the risk of macrovascular disease in this people, an understanding of the alterations in the major lipids that occur due to the broad range of antidiabetic medications may enhance our approach to drug selection for the better treatment of type 2 diabetes.

Keywords: Dyslipidemia, High density lipoproteins (HDL), Low density lipoproteins (LDL), Triglycerides, Type2 diabetes mellitus (T2DM)

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INTRODUCTION

Diabetes mellitus (DM) is a global public health problem. It is estimated that there are more than 220 million diabetics worldwide. The World Health Organization estimates that the ***number*** of people with diabetes in ***the world*** would reach 300 million by 2025[1,2]. It is well known that diabetes and hypertension are major risk factors in the development of nephropathy, retinopathy, and specifically cardiomyopathy progressing to myocardial infarction. Patients with T2DM characteristically have fasting hyper-triglyceridemia and exaggerated dyslipi-daemia [3,4]. Therefore, a diet reducing lipids concentrations would be useful in preventing atherosclerosis-like cardiovascu-lar events associated with T2DM.

Dietary saturated fatty acids (SFA) increase the risk for cardiovascular disease, whereas monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) decrease those risks by the modification of lipids. In the past two decades there has been a significant increase in the number of drugs available to treat the hyperglycaemia of type2 diabetes, and five different types of oral antidiabetic agents are currently available. It is hypothesized that all classes of oral antidiabetic drugs have significant lipid lowering effect along with glycemic control effect.

Current oral anti-diabetic agents: Effects on lipid profile

There remain five classes of oral antihyperglycemic drugs approved by the U.S. Food and Drug Administration (FDA)

Biguanides (*METFORMIN*)

Metformin is a biguanide currently prescribed as an oral antihyperglycemic agent. Metformin is an effective oral antidiabetic drug. Metformin is a drug of choice for the treatment of overweight and obese Type 2 diabetic patients. Notably, metformin has other nonglycemic benefits including modest lowering of lipid levels and improvements in fibrinolysis, inflammatory markers, and platelet antiaggregating effect.

The biguanides act both by inhibiting hepatic gluconeogenesis and increasing peripheral insulin sensitivity [5,6]. Metformin leads to a decrease in HbA1C values by 1.5-2.0%. And also metformin has a particularly beneficial effect on plasma lipid causing a decrease in triglycerides and LDL-cholesterol by approximately 10–15%. HDL levels may increase slightly or remain unchanged, and typically there is a modest weight loss (2–3 kg) associated with metformin therapy

Few studies, [7-9] have shown beneficial effect of metformin on BP, although the evidence for this is inconsistent. The literature shows discrepant results about the influence of metformin on lipid profile. Some studies reported that there is a reduction only in TC levels [10,11] , while others reported a reduction in TC and TG with an increase of HDL-C. Another investigation showed an association of metformin with an improvement in the lipid profile even in non-diabetic patients. New studies have suggested metformin shows beneficial in improving biochemical indices in patients with NAFLD. Nevertheless, the use of metformin could still be beneficial in this group as it is associated with a reduction in serum levels of lipids and glucose.

Sulfonylureas (SU)

First generation: chlorpropamide, tolazamide, tolbutamide

Second generation: glibenclamide, glipizide, glyburide, gliclazide, and glimepiride

Sulfonylureas have represented the backbone of oral therapy in non-insulin dependent diabetes mellitus for more than 30 years. Despite this, our knowledge about the mode of actions of these agents is limited, and the use of them is far from rational. Sulfonylureas acts primarily by stimulating insulin secretion. The evidence for clinically significant extrapancreatic effects is scanty. Therefore, the effect of sulfonylurea is limited to patients with preserved β–cell function [12]. Sulfonylureas are very effective in combination rather than monotherapy.

Table 1: Percentage Decrease in Plasma Lipids Levels in Diabetic Patients taking Sulfonylureas in Combination

Parameters	Met+Glim[13]	Met+Glib[13]	SU+Pio[14]	Met+Gyl[15]
Total Cholesterol	↓16%	↓11%	↓5%	↓2%
Triglycerides	↓12%	↓13%	↓15%	↓4%
LDL	↓10%	↓14%	↑2%	↓3%
HDL	↑15%	↑5%	↑13%	↑5%

Keywords: Met: Metformin, Glib: Glibenclamide, Glim: Glimipiride, SU: Sulfonylureas, Gyl: Glyburide

As mentioned in the table 1, lipid values were decreased significantly while HDL-C values were increased at the same time. Sulphonylureas in combination with metformin were observed to shown significant effect. To be specific metformin and glimepiride group has a good favourable effect on lipids as compared to the metformin and glibenclamide group. In combination of SU with glitazone doesnot show much favourable effect on plasma lipids.Thus these studies reveal that sulfonylureas in combination with metformin have a beneficial effect on lipid profile.

Thiazolidinediones

Pioglitazone, Rosiglitazone, Troglitazone

The thiazolidinediones are insulin sensitizers that bind to PPAR-gamma receptors, which are nuclear transcription factors that modulate gene expression, leading to increased glucose transporter expression [16]. Rosiglitazone and pioglitazone were the first agents in this

class to get approval. Troglitazone, was removed from the market in 2000 due to hepatotoxicity. Around the same time rosiglitazone and pioglitazone commenced marketing in the US[17]. Around 2007-08, few meta-analysis suggested that long term use of thiazolidinediones may increase the risk of myocardial infarction [18,19]. Few similar meta analyses recently suggested that pioglitazone, the other approved thiazolidinedione, was not found to increase cardiovascular risk [20,21]. Thus, unlike rosiglitazone, pioglitazone does not seem to be associated with increased cardiovascular risk. However, like rosiglitazone, pioglitazone does not increase the risk of new-onset heart failure, but worsen pre-existing heart failure [22]. Hence thiazolidinediones should be avoided in patients with congestive heart.

Table 2: Percentage Decrease in Plasma Lipids Levels in Diabetic Patients taking Thiazolidinediones in Combination

Parameters	Trog[23]	Met+Rosi[24]	Met+Pio[25]	Ins+Trog[26]	Trog+SU[27]
Total Cholesterol	↓2%	↓2%	↓1%	↑1%	↓4%
Triglycerides	↓21%	↓1%	↓5%	↓14%	↑4%
LDL	↓1%	↓3%	↓6%	↑8%	↓3%
HDL	↑9%	↑6%	↑9%	↑5%	↑5%

Keywords: Met: Metformin, Rosi: Rosiglitazone, Pio: Pioglitazone, Trog: Troglitazone, Ins: Insulin, SU: Sulfonylureas

As mentioned in the table thiazolidinediones are effective in combination than monotherapy. It has favourable effects on lipid profile in combination with metformin, were there is a decrease in the levels of LDL, Triglycerides and an appreciable increase in HDL levels.

Alpha-Glucosidase inhibitors

Acarbose,Miglitol,Voglibose

Acarbose, miglitol and voglibose are the α -glucosidase inhibitors currently available. They act by inhibiting the intestinal enzyme that breaks down polysaccharides into monosaccharides. Because the polysaccharides are poorly absorbed from the gastrointestinal tract, the effect of these drugs is to delay intestinal absorption of carbohydrate and particularly attenuating postprandial blood glucose elevations[28,29].The primary side effect of α -glucosidase inhibitors is flatulence and other gastrointestinal symptoms. Impaired absorption of carbohydrate leads to increased arrival of carbohydrate in the colon, which can cause considerable gas production, diarrhoea, and abdominal pain. They are less effective than the agents described above (HbA1C declines approximately 1%), with a predominant effect on post-prandial glucose levels. A slight decrease in triglyceride levels has been demonstrated without any significant change in HDL, LDL, or body weight[30-32].

Meglitinides

Repaglinide, Nateglinide

The glinides are non-sulphonylurea insulin secretagogues that act by targeting post-prandial hyperglycaemia. They act by binding to the sulfonylurea receptor and inducing depolarization of the β-cells. They also have shorter half-lives than sulfonylureas; therefore, they require more frequent dosing. They usually tend to be less potent than sulfonylureas, lowering A1C by ~ 1–1.5 percentage points[33]. The efficacy of this class of drug is reportedly similar to that of a sulphonylurea or metformin.[34] Glinides has no significant effect on plasma lipid as monotherapy, but shows beneficial effect in combination therapy as shown in the table below.

DPP-IV Inhibitors(Dipeptidyl peptidase-IV inhibitors)

Sitagliptin, Saxagliptin, Vildagliptin, Linagliptin, Teneligliptin

DPP-IV inhibitors are the newest class of oral agents for the treatment of type 2 diabetes. They act by inhibiting the enzymatic degradation of glucagon-like peptide 1 (GLP-1). GLP-1 is an incretin hormone produced by the distal small intestine and released into the bloodstream.

GLP-1 acts to delay gastric emptying, suppress glucagon release, and increase glucose-stimulated insulin release. It may also act to increase satiety. The resulting effect of GLP-1 is to limit postprandial hyperglycemia, but the half-life after secretion into the blood is very short. Use of DPP-IV inhibitors increases levels of endogenously produced GLP-1 and thereby decreases postprandial glucose excursions [39].

Table 3: Percentage Decrease in Plasma Lipids Levels in Diabetic Patients taking Meglitinides in Combination

Parameters	Repa+pio [35]	Repa+Met [36]	Nate [37]	Repa [38]
Total Cholesterol	↓3%	↓17%	↓7%	↑3%
Triglycerides	↓21%	↓27%	↓12%	↓5%
LDL	↓8%	↓24%	↓9%	↓5%
HDL	↑11%	↑12%	↑10%	↑16%

Keywords: Met: Metformin, Repa: Repaglinide, Pio: Pioglitazone, Nate: Nateglinide

A few retrospective analyses suggest that patients with T2DM treated with the DPP-4 inhibitor, sitagliptin showed decreases in LDL cholesterol, total cholesterol, and triglyceride levels [40]. Other studies in patients with T2DM treated with the DPP-4 inhibitors sitagliptin and vildagliptin reported decreases in levels of total cholesterol, LDL cholesterol, and triglycerides and an increase in HDL cholesterol [41,42].

DPP-IV inhibitors induces improvements in blood pressure and lipids, hence they are helpful in patients with preexisting cardiovascular disease [43,44]. The administration of DPP-4 inhibitors reduces postprandial triglyceride levels in humans, however, its effects on postprandial free fatty acid levels are a matter of debate.[45-48] DPP-4 inhibitors have some cardiovascular protective effects in T2DM in addition to their antidiabetic actions. Additional benefits include lowering the blood pressure, improving the lipid profile and the endothelial dysfunction, decreasing the macrophage-mediated inflammatory response, and reducing myocardial injury.

Glucagon – like peptide 1 (GLP - 1) receptor agonists

Exenatide, Liraglutide

GLP-1 agonists are the new class of drug which targets the adverse effects of type 2 diabetes mellitus. GLP-1 is an incretin hormone produced by the distal small intestine and released into the bloodstream. GLP-1 acts to delay gastric emptying, suppress glucagon release, and increase glucose-stimulated insulin release. Thereby GLP-1 decreases postprandial glucose excursions.

Short-acting exenatide; it is approved for monotherapy or as part of combination therapy. Clinical trials shows that exenatide 5μg to 10 μg injected subcutaneously twice a day lowers HbA1c levels. The most potent glucose-lowering effects occurred when exenatide was used in combination with metformin and a thiazolidinedione [49,50].

Liraglutide is the first of the long acting GLP-1 agonists, administered subcutaneously once a day. Liraglutide has been studied in combination with metformin, [51] sulfonylureas, [52] thiazolidinediones plus metformin, [53] and metformin plus sulfonylureas [54,55]. As a longer-acting agent, more profound reductions in HbA1c levels have been observed. Liraglutide resulted in statistically significant better glucose lowering without the risk of hypoglycemia or weight gain. Both exenatide and liraglutide are associated with weight loss when used as monotherapy or as part of combination therapy strategies. Glucagon-like peptide-1 agonists also have beneficial effects on blood pressure [56,57]. Lipid effects are more beneficial. Significant improvements in very low-density lipoprotein, free fatty acids, and triglycerides have been observed [58].

Emerging nutritional supplements

Sesame oil and Olive oil

Recent studies have reported that sesame oil and olive oil exhibits favourable effect on lipid profiles. The vegetable oils such as olive and sesame can improve lipid profiles, but there is no difference observed between two

oils. A daily 25-mL dose of all types of olive oil, reduced lipid cardiovascular risk-factors, and improved glutathione antioxidant status. Daily consumption of high- and medium-polyphenol olive oil decreased oxidative damage on lipids. Consumption of olive oil with high phenolic content provided the greatest benefits by increasing HDL cholesterol levels and reducing the oxidative damage on lipids[59]. Sesame oil is rich in poly and monounsaturated fatty acids, such as sesame lignans like sesamin and episesamin that modulate cholesterol metabolism by inhibiting the synthesis and absorption of cholesterol [60,61]. The lignans present in sesame oil may play a role in the improvement of lipid profileIt induces expression of aldehyde dehydrogenase (an alcohol-metabolizing enzyme) gene, as a result the sesamin regulate metabolism of lipid[62].Also there are studies which report that the sesame oil protects against fibrosing steatohepatitis by inhibiting matrix metalloproteinases-2, 9(MMP-2, 9) activities, up-regulating tissue inhibitor of matrix metalloproteinases(TIMP-1 expression), and peroxisome proliferator-activated receptor (PPAR-γ)[63].

Garlic

Garlic (Allium sativum) holds a unique position in history and is recognized for its therapeutic potential. Extensive research work has been carried out on the health promoting properties of garlic, often referred to its sulfur containing metabolites i.e. allicin and its derivatives[64,65]. It also provides cardiovascular protection mediated by lowering of cholesterol, blood pressure, anti-platelet activities, and thromboxane formation thus providing protection against atherosclerosis and associated disorders. It has been shown to reduce blood sugar and has lipid lowering properties in various animal and clinical studies. Thus, it can be analysed from various studies that garlic has been shown to demonstrate antihyperglycaemic and lipid lowering effect in patients of diabetes mellitus and obesity. Metformin and garlic both showed beneficial effect on lipid profile parameters. However, fall in total CHL, TG, LDL and an increase in HDL were more pronounced with garlic. Conclusively, though metformin and garlic were effective in lowering FBG, HbA1c and lipid profile, yet garlic showed better results as an antihyperglycaemic and lipid lowering agent as an adjunct to metformin. Also garlic showed protective effect on non-alcoholic fatty liver disese (NAFLD) due the active ingredient s-allylmercaptocysteine present in garlic [66].

Mango (*Mangifera indica*)

Mangos are well known for their antibacterial, antiviral and anticancer properties, but few studies also report that mango helped to regulate glucose and lipids. The mango flesh contains polyphenols, terpenoids, carotenoids, fatty acids [67,68] and other trace elements such as calcium, vitamin A and vitamin C [69]. Significant reductions in plasma glucose concentration is due to mangiferin. Mangiferin exhibited a hypolipidemic effect by significant reductions in plasma total cholesterol, triglycerides, and LDL concentrations along with an increase of HDL-cholesterol [70]. The mangiferin present in mango also act as anti-steatotic agent and protects from NAFLD [71].

CONCLUSION

The effects of common antidiabetic medications on lipid levels are summarized. Metformin in combination with sulphonylureas, and metformin in combination with meglitinides have negligible effects on plasma lipids. The thiazolidinediones cause an elevation in HDL and variable increase in LDL, with no change in the HDL:LDL ratio. Combination of any two class of anti-diabetic drug shows favourable effect on plasma lipids rather than monotherapy. Specifically, metformin and sulfonylureas combination have appreciable effect on plasma lipids.

Overall, the impact of antidiabetic medications on traditional plasma lipid classes is moderate, however there may be added benefit in lipid subclass distribution. Patients with diabetic dyslipidaemia are unlikely to achieve cholesterol and triglyceride targets without supplemental specific lipid-lowering drugs.

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