ATHEROGENIC DIABETIC DYSLIPIDEMIA

Abstract

Diabetes is a widely prevalent condition and steadily growing as well. In Indian type 2 diabetic patients have a higher amounts of TG and atherogenic lipid sd-LDL. Atherogenic diabetic dyslipidemia is associated with higher residual CV risk and should be treated with a statin as first-line agent. A common outcome of such a body composition and dyslipidemia in Asian Indians is the tendency to develop insulin resistance. Diabetic Dyslipidemia (DD) consists of specifically mild to a marked elevation of triglyceride-rich lipoproteins, very low-density lipoprotein-cholesterol (VLDL-C) and VLDL-C remnants, and low levels of HDL. Along with lifestyle modifications, statins are considered as first-line therapy for diabetic dyslipidemia. Statins are capable of decreasing LDL-C levels by as much as 50%. They may have additional benefits on HDL-C and TG levels.

Keywords: Diabetes, lipoprotein, dyslipidemia, Cardiovascular diseases

Introduction:

India accounts for 21% of the world's global burden of disease, where non-communicable diseases (NCDs) are responsible for two-thirds of the total morbidity burden and about 53% of total deaths in India. Two out of four leading NCDs in India are[1], Cardiovascular diseases (CVDs) & Diabetes Mellitus (DM). Diabetes is one of the major risk factors for the development of Dyslipidemia and CVD. As per International Diabetes Federation (IDF)-2021, India is ranking 2nd globally in the incidence of DM with a patient population of 74.2 Million.[2] Major associated co-morbid condition of diabetes is dyslipidemia, and it is known as diabetic dyslipidemia. As per ICMR – INDIAB study[3] 2014, 79% of Indian population had dyslipidemia and more importantly 9 out 10 Indian diabetes patients were dyslipidemic. Unlike western population, most common dyslipidemia pattern in India was low high density lipoprotein (HDL) - 72.3%, High triglycerides (TG) - 29.5% and followed by high low density lipoprotein (LDL) - 11.8%. This study showed significant evidence of high prevalence of low HDL and high TG in India.

Atherogenic Diabetic Dyslipidemia (ADD):

Diabetic Dyslipidemia (DD) consists of specifically mild to a marked elevation of triglyceride-rich lipoproteins, very low-density lipoprotein-cholesterol (VLDL-C) and VLDL-C remnants, and low levels of HDL. In addition, LDL particles are converted to smaller, perhaps more atherogenic, lipoproteins termed 'small dense LDL-C' (sd-LDL-C).[4] This combination of hypertriglyceridemia, low HDL-C, and high levels of sd-LDL-C, better addressed as Atherogenic Diabetic Dyslipidemia (ADD), is particularly seen in Asian Indians.[26] Krishnamurthy V et al showed that in Indian diabetes patients prevalence of ADD was seen in 34.2% and raised non-HDL cholesterol in 73.3%., which was more significantly associated with poor glycemic control (HbA1c >8%).[5]

Although the precise reason for such dyslipidemia is unknown, genetic predisposition and characteristic body composition (excess intra-abdominal fat) may be important contributors. A common outcome of such a body composition and dyslipidemia in Asian Indians is the tendency to develop insulin resistance.[6] This condition is majorly responsible for the development of coronary artery disease (CAD), which is 2-4 times higher in diabetic subjects, and in Indians, CAD occurs prematurely, i.e. one to two decades earlier than in the West.

Pathogenesis of ADD:

Insulin resistance (IR) is primarily responsible for the pathogenesis of ADD in T2DM. IR at the adipose tissue results in an increased release of free fatty acids (FFA) into circulation through disinhibiting lipase enzymes. Increased FFA flux and apolipoprotein B (Apo B) production in the liver stimulate increased secretion of very low-density lipoprotein cholesterol (VLDL-C), resulting in hypertriglyceridemia. In addition, cholesterol ester transport protein (CETP) stimulates the exchange of cholesteryl esters from both HDL-C and low-density lipoprotein cholesterol (LDL-C) to VLDL-C. [27] TG-enriched HDL-C is easily metabolized by lipases and leads to reduce the availability of HDL-C for reverse cholesterol transport. TG-enriched, low-density lipoprotein cholesterol (LDL-C) can also undergo lipolysis and become smaller and denser, known as sdLDL-C. Low levels of HDL-C and the presence of sdLDL-C are each independent risk factors for CVD.[7]

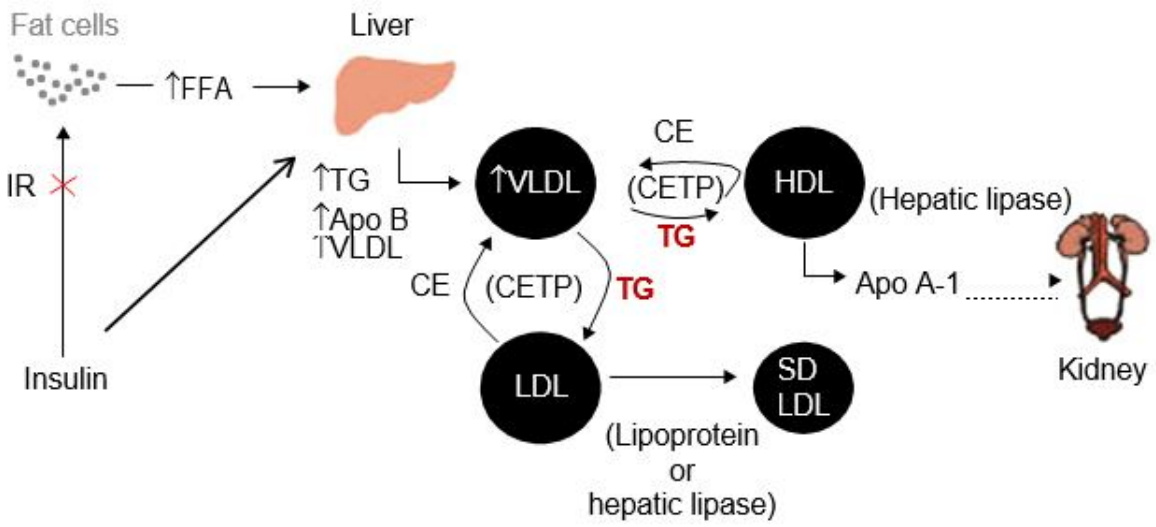

Figure 1 Pathogenesis of ADD.

Abbreviations: *ADD, atherogenic dyslipidemia of diabetes; iR, insulin resistance; FFA, free fatty acids; TG, triglycerides; Apo B, apolipoprotein B; vLDL, very low density lipoprotein; Ce, cholesteryl esters; CeTP, cholesterol ester transport protein; LDL, low density lipoprotein; HDL, high density lipoprotein; Apo A-1, apolipoprotein A1; SDLDL, small dense low density lipoprotein*

ADD including elevated TG and increased CV risk

Several large trials and meta-analyses have investigated the effects of lipid-lowering statin therapy and have consistently demonstrated that statin therapy significantly reduces LDL-C levels and the incidence of CV events. Despite the efficacy of statin therapy in these studies, statins did not eliminate CV risk. Rather, significant residual CV risk remains after treatment with statins, especially in high-risk patients such as those with diabetes. Residual CV risk stems, at least partially, from low HDL-C and elevated TG. With elevated TG levels, a combination of LDL-C with VLDL-C in the measure of non-HDL-C may be a better predictor of CV risk than LDL-C alone.[8]

Data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial was used to determine the association between TG levels and outcomes in patients with T2DM and CAD.[9] In fully

adjusted analyses of 2,307 patients, every 50 mg/dL increase in TG level was associated with a 3.8% (Hazard Ratio (HR) 1.038, p <0.001) increase in the major adverse cardiovascular events (MACEs) and a 6.4% (HR 1.064, p <0.001) increase in the secondary outcome as well; which suggested independent association of TGs with MACEs in DM patients with CAD.

Castañer O et al. (2020); evaluated the association of triglycerides and remnant cholesterol (remnant-C) with MACEs in older individuals at high CV risk. In the high-risk primary prevention PREDIMED (Prevención con Dieta Mediterránea) trial population of 6,901 patients, after a median follow-up of 4.8 years; it was observed that TGs (HR: 1.04; per 10 mg/dl [0.11 mmol/l]; p < 0.001), non-HDL-C (HR: 1.05; per 10 mg/dl [0.26 mmol/l]; p < 0.026), and remnant-C (HR: 1.21; per 10 mg/dl; p < 0.001), but not LDL-C or HDL-C, were associated with MACEs.[10]

International Guidelines Recommendations on high TG management: It is justified to target TG as a vascular risk factor because of the role of TG-rich lipoproteins in atherogenesis. Evidence supports a potential role for TG as vascular risk factor, owing in part to the accompanying burden of atherogenic remnant particles, sd-LDL-C, reduced HDL-C, and a high frequency of accompanying insulin resistance. TG-associated CVD risk occurs even in subjects with low LDL-C, and lowering both lipids provides greater benefit than reducing LDL-C alone.[11]

Recently international guidelines by the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) recommended hypertriglyceridemia in high-risk patients should be managed with TG lowering agents[12]. ESC/EAS 2019 guideline on the management of dyslipidemia recommends no goal for TG level, but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors. In high-risk (or above) patients with TG levels between 1.5-5.6 mmol/L (135-499 mg/dL) despite statin treatment, TG lowering drugs [n-3 PUFAs (icosapent ethyl 2*2 g/day)] should be considered in combination with a statin. In primary prevention patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), TG lowering drugs (fenofibrate or bezafibrate) may be considered in combination with statins.[13,14]

Management of Atherogenic Diabetic Dyslipidemia (ADD):

Along with lifestyle modifications, statins are considered as first-line therapy for diabetic dyslipidemia. Statins are capable of decreasing LDL-C levels by as much as 50%. They may have additional benefits on HDL-C and TG levels. These medications may be used in monotherapy, or they may need to be used in

combination for the patient with multiple lipid abnormalities in addition to high LDL-C, like high TG and low HDL-C.[15]

Role of Fibrates: The peroxisome proliferator-activated receptor-α (PPAR-α) agonists are beneficial in the treatment of ADD, lowering TG, and raising HDL-C levels, though with minimal impact on LDL-C. Outcome studies like FIELD, and ACCORD have shown that fabric acid derivatives are especially effective drugs in decreasing CV events in patients with diabetes given the lipid derangements are in TG and HDL-C levels. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study sub-analysis of those patients who had high TG or high TG + low HDL-C, a significant reduction in CV events was observed.[16] Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial data, together with post hoc analyses of three other fibrate trials, suggests that when TG is >200 mg/dL and HDL-C is <35 mg/dL after statin therapy has significantly reduced LDL-C levels, fibrate treatment can be considered.[17] Fibrates are commonly associated with adverse events like myalgia, myopathy, and renal impairment; especially when prescribed along with statins.

Other TG lowering agents: Niacin is recommended in patients with hypertriglyceridemia and low HDL-C. But in the current era of statin, niacin has not manyany roles to treat dyslipidemia patients. Niacin may potentiate insulin resistance, so its usage is limited in ADD.[18] Omega-3 fatty acids are also commonly used in Western countries, but their effects on residual risk in statin-treated diabetic patients are not clear.[16] Moreover, high doses (2–4 g/day) and the prevalence of strict vegetarian diets in India preclude the use of these drugs.

Role of dual PPAR α/γ agonists in ADD:

Peroxisome proliferator-activated receptors (PPAR) α/γ agonists can play a vital role in the management of ADD post statin therapy. Dual PPAR receptor agonism leads to improvement of insulin sensitivity in adipose tissue and increases fatty acid uptake in liver and adipose tissue, resulting in the reduction of elevated triglyceride.[18]

Many such dual PPAR agonists have been developed in the past and have failed in clinical trials, due to lack of efficacy or safety concerns; while Saroglitazar is the only approved molecule from this group. Table 1 outlines the details of such molecules.[19]

Table 1: Dual PPAR α/γ agonists and clinical development

Compound	Targeted disease	Current Status
Muraglitazar	Metabolic disorders, type 2 diabetes	Discontinued in 2006 due to adverse Cv events (myocardial infarction, stroke, heart failure, and transient ischemic attack)
Ragaglitazar	Type 2 diabetes	Discontinued in 2004 due to weight gain, oedema, anemia, and urothelial cancer
Tesaglitazar	Type 1 diabetes, type 2 diabetes, cardiac arrhythmia, and lipid metabolic disorder	Discontinued in 2006 due to elevated creatinine, lowered GFR, weight gain, anemia, and leukopenia
Naveglitazar	Cardiovascular disease, Dyslipidemia, and type 2 diabetes	Further development has been stopped
Farglitazar	Type 2 diabetes	Discontinued in 2003
imiglitaazar	Type 2 diabetes	Discontinued in 2004 due to abnormalities in liver enzyme tests
Aleglitazar	Type 2 diabetes	Discontinued in 2013 due to adverse events like heart failure, gastrointestinal bleeding, and renal dysfunction
Saroglitazar	High TG in Type 2 diabetes	Received an approval from DCGI in 2013 in India

Abbreviations: CV, cardiovascular; DCGI, Drug Controller General of India; PPAR, peroxisome proliferator activator receptor; GFR, glomerular filtration rate; TG, Triglyceride

Saroglitazar: A First Novel Dual PPAR α/γ receptors agonist

Peroxisome Proliferator-Activated Receptors (PPARs) are nuclear lipid-activated transcription factors that regulate the expression of genes involved in the control of lipid and lipoprotein metabolism, glucose homeostasis, and inflammatory processes. PPAR-α is implicated in the uptake and oxidation of fatty acids (FAs) and lipoprotein metabolism, while PPAR-γ agonism has beneficial effects on glucose homeostasis by increasing insulin sensitivity and glucose disposal and prevent the loss of beta cell mass in the pancreas. PPAR-α agonists like fibrates are effective in managing lipids and PPAR-γ agonists are insulin sensitizers that control hyperglycemia in T2DM[20], by using dual PPAR-α/γ agonists one can control both the lipid and glucose levels simultaneously. Saroglitazar is a non-TZD and non-fibrate molecule belongs glitazar class compound is designed as a dual PPAR-α/γ agonist having a strong PPAR-α effect with moderate PPAR-γ effect. Saroglitazar is a potent and predominantly PPAR α agonist with moderate PPAR γ agonistic activity. PPARs are nuclear lipid-activated transcription factors that regulate the expression of various genes involved in the control of lipid and lipoprotein metabolism, glucose homeostasis, and inflammatory processes. The pharmacological effects of Saroglitazar were extensively evaluated in various preclinical models. Saroglitazar showed both anti-dyslipidemic and anti-diabetic effects mainly mediated via activation of both PPAR receptors respectively.[18]

Saroglitazar has been investigated in various indications like hypertriglyceridemia in T2DM, Non alcoholic fatty liver disease (NAFLD), Type 2 Diabetes Mellitus, etc. In the euglycemic clamp study of Saroglitazar, insulin sensitivity and glucose metabolism were increased in Type 2 DM patients with high

TG, which supports Saroglitazar as an insulin sensitizer agent.[21] In Phase III clinical trials of PRESS V & PRESS VI, Saroglitazar showed a significant reduction of elevated TG up to 45% from baseline after 3-6 months of therapy. [22,23] As per the recently published Saroglitazar Integrated Review Analysis of ~ 5,800 diabetic dyslipidemia patients by Kaul U et al.; Saroglitazar has shown a reduction in TG in the range from 45-62%, HbA1c from 0.7-1.6% and sd-LDL by 20.3%.[24] In P-III clinical trials and observational studies; Saroglitazar is found to be safe with minor side effects in patients with T2DM. In 2020[25], Saroglitazar biopsy-driven study in NAFLD was published, whereit has shown significant improvement in liver fat, liver enzymes, and fibrotic conditions as well. Based on this clinical data, Saroglitazar has become the first approved drug for NAFLD management in India by the Drug Controller General of India (DCGI). NAFLD is such a widely prevalent condition globally and in India as well, but current management rate of this disease is very low. There is a need to develop guideline based multidisciplinary approach for NAFLD management, with usage of approved medications like Saroglitazar. Saroglitazar is only approved in India for management of ADD and NAFLD. Global approval of this molecule will certainly be supportive for managing such metabolic conditions.[28]

Conclusion: Diabetes is a widely prevalent condition and steadily growing as well. In Indian type 2 diabetes patients have a higher amount of TG and atherogenic lipid sd-LDL. Atherogenic diabetic dyslipidemia is associated with higher residual CV risk and should be treated with a statin as first-line agent. To control TG after statin therapy, currently, many options are available, including Saroglitazar; as an efficacious and safe option.

COMPETING INTERESTS DISCLAIMER:

The authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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