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The nuances of atherogenic dyslipidemia in diabetes: Focus on triglycerides and current management strategies


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A B S T R A C T

Diabetes mellitus (DM) is a pandemic disease and an important cardiovascular (CV) risk factor. The atherogenic dyslipidemia in diabetes (ADD) is characterized by high serum triglycerides, high small dense LDL levels, low HDL levels and postprandial lipemia. Insulin resistance is a primary cause for ADD. Though statins are highly effective for CVD prevention in DM but a significant residual CV risk remains even after optimal statin therapy. Fibrates, niacin and omega-3 fatty acids are used in addition to statin for treatment of ADD (specifically hypertriglyceridemia). All these drugs have some limitations and they are far from being ideal companions of statins. Many newer drugs are in pipeline for management of ADD. Dual PPAR α/γ agonists are in most advanced stage of clinical development and they have a rational approach as they control blood glucose levels (by reducing insulin resistance, a primary factor for ADD) in addition to modulating ADD. Availability of dual PPAR α/γ agonists and other drugs for ADD management may improve CV outcomes and decrease morbidity and mortality in diabetic patients in future.

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1. Introduction

Diabetes mellitus (DM) is a global epidemic and important cause of morbidity and mortality. As per International Diabetes Federation (IDF) estimate, 366 million people worldwide had DM in 2011; by 2030, this number will increase to 552 million.1 Being a highly populated country, India also has a large population suffering from DM. The Indian Council of Medical Research–India Diabetes (ICMR–INDIAB) study had extrapolated its phase I results in 2011, which estimates 62.4 million individuals with diabetes and 77.2 million with pre-diabetes in India.2
Today, DM is considered one of the most important cardiovascular disease (CVD) risk factors and even considered as an equivalent to myocardial infarction. Dyslipidemia is also considered as very important CVD risk factor. Most of diabetic patients have some kind of dyslipidemia. As per an Indian study, 85.5% of men and 97.8% of women in India with type 2 diabetes mellitus (T2DM) have concomitant dyslipidemia. Presence of T2DM and dyslipidemia both increase the CV risk by 3–4 times compared to non-diabetic patients with dyslipidemia. Statins are very commonly used in diabetic patients and they reduce CVD risk by 20–30%. The residual CVD risk (70–80%) can be due to other risk factors like sedentary lifestyle, smoking, hypertension, psychological stress, atherogenic dyslipidemia, low HDL levels, etc. Addressing these risk factors is important for the further reduction of CVD risk in diabetic patients.

2. Atherogenic dyslipidemia in diabetes (ADD)

The most common pattern of dyslipidemia in type 2 diabetic patients is atherogenic dyslipidemia which is characterized by elevated triglycerides (TGs), raised small dense LDL (sdLDL) levels and decreased HDL cholesterol levels.

In 1990, Austin et al first described a risk-conferring lipid/lipoprotein profile, termed “atherogenic dyslipidemia” or the “atherogenic lipoprotein phenotype” that comprises a higher proportion of sdLDL particles, reduced HDL-C, and increased TGs. Atherogenic dyslipidemia is characteristically seen in patients with obesity, the metabolic syndrome, insulin resistance, and T2DM and has emerged as an important marker for the increased CVD risk observed in these populations.

As shown in Fig. 1, Insulin resistance (IR) is primarily responsible for the development of ADD in T2DM. IR at the adipocyte results in increased release of free fatty acids (FFA) into the circulation. A similar accumulation of fatty acids could arise from defects in fatty acid transporters or intracellular binding proteins. Increased FFA flux to the liver stimulates the assembly and secretion of very low density lipoprotein (VLDL) resulting in hypertriglyceridemia. In addition, VLDL stimulates the exchange of cholesteryl esters from both HDL and LDL for VLDL TG. Apo AI can dissociate from TG-enriched HDL. This free apo AI is cleared rapidly from plasma, in part by excretion through the kidney, thus reducing the availability of HDL for reverse cholesterol transport. TG-enriched LDL can undergo lipolysis and become smaller and denser. Low levels of HDL and the presence of small dense LDL are each independent risk factors for cardiovascular disease.

Thus, hypertriglyceridemia is the initial lipid abnormalities leading to others in ADD. Various studies have shown high prevalence of hypertriglyceridemia in T2DM. In a prescription audit in UK on 14652 diabetic patients who are already on statin therapy, 46.3% of patients have hypertriglyceridemia (TG >150 mg/dl). In a cross sectional study in 702 diabetic patients, 83% of patients had hypertriglyceridemia. In the 11-year follow-up of the Paris Prospective Study, hypertriglyceridemia (but not hypercholesterolemia) predicted CHD mortality in a combined group of subjects with impaired glucose tolerance and diabetes.

Addressing the hypertriglyceridemia can reduce the further lipid abnormalities in T2DM patients. Here we discuss the pathogenesis and management of hypertriglyceridemia in ADD.

3. Hypertriglyceridemia in ADD and atherosclerosis

Consequences of hypertriglyceridemia in ADD which promotes atherosclerosis are mentioned in Table 1. TGs, represents an important biomarker of CVD risk because of their association with atherogenic remnant particles and Apo CIII, a proinflammatory, proatherogenic protein found on all classes of the plasma lipoproteins. Several species of triglyceride-rich lipoproteins (TRLs) including VLDL and VLDL remnants, as well as chyomicron (CM) remnants appear to promote atherogenesis independently of LDL. Remnant species result from partial hydrolysis by lipoprotein lipase (LPL) of TRLs of hepatic and intestinal origin that have picked up cholesterol esters from HDL through the action of cholesterol ester transfer protein (CETP) resulting in hypertriglyceridemia. In addition, VLDL stimulates the exchange of cholesteryl esters from both HDL and LDL for VLDL TG. Apo AI can dissociate from TG-enriched HDL. This free Apo AI is cleared rapidly from plasma, in part by excretion through the kidney, thus reducing the availability of HDL for reverse cholesterol transport. TG-enriched LDL can undergo lipolysis and become smaller and denser. Low levels of HDL and the presence of small dense LDL are each independent risk factors for cardiovascular disease.

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Fig. 1 – Pathogenesis of ADD (IR, insulin resistance; CE, cholesteryl ester, CETP: cholesterol ester transport protein, TG: triglycerides, Apo B: apolipoprotein B, VLDL: very low density lipoprotein, FFA: free fatty acids, LDL: low density lipoproteins HDL: high density lipoproteins, Apo A: apolipoprotein A).
Table 1 – Consequences of hypertriglyceridemia.16

- Low levels of HDL-C
- The presence of small, dense LDL particles
- The presence of atherogenic triglyceride-rich lipoprotein remnants
- Insulin resistance
- Increases in coagulability and viscosity
- Proinflammatory status

4. Hypertriglyceridemia and CV risk

Individual epidemiologic studies have shown variable results regarding the strength of association between hypertriglyceridemia and CHD, specifically after adjusting for the presence of associated risk factors such as insulin resistance and low HDL-C levels which are components of ADD.71 Therefore, meta-analysis has been crucial to distinguish hypertriglyceridemia as an independent risk factor from a risk marker of associated conditions such as those in the metabolic syndrome.

In 2007, Sarwar et al.22 performed a large meta-analysis of 29 prospective studies from Western populations and reported an odds ratio of 1.7 (70% increased risk) comparing the risk of CHD for those in the upper to lower tertiles of the TG distribution after adjusting for other risk factors. This study found no difference between men and women in the strength of association. A similar odds ratio (1.7) was reported in a meta-analysis that included data from 26 prospective studies regarding the strength of association between hypertriglyceridemia and CHD, specifically after adjusting for one other CV risk factor (hypertension, albuminuria, etc) irrespective of lipid profile.30 Statins also lower TG levels and increase HDL modestly.31 Trials of statin monotherapy found that increased baseline TG levels predicted worse CVD outcomes and that statins reduced CVD better in patients who had high baseline TGs.34 This provides a rationale

5. Current therapies for hypertriglyceridemia in diabetes

Various drug therapies available for hypertriglyceridemia are used in diabetic patients to control high TGs.

6. Non-pharmacological management

Nutrition measurements that affect serum triglycerides levels include body weight status; body fat distribution; weight loss; the macronutrient profile of the diet, including type and amount of dietary carbohydrate, fat and alcohol consumption. Importantly, multiple interventions can yield additive triglyceride-lowering effects that can result in significant reductions in triglyceride levels.

- A weight loss of 5%–10% results in a 20% decrease in triglycerides, approximately a 15% reduction in LDL-C, and an 8%–10% increase in HDL-C.24 Meta-analyses have reported that for every 1 kg of weight loss, triglyceride levels decrease 1.9%, or 1.5 mg/dL.25
- A weight loss of 5%–10% results in a 20% decrease in triglycerides, approximately a 15% reduction in LDL-C, and an 8%–10% increase in HDL-C.24 In a meta-analysis, a moderate-fat diet (32.5%–50% of calories from fat) versus a lower-fat diet (18%–30% of calories from fat) resulted in a decrease in triglyceride level of 9.4 mg/dL (P < 0.00001) in those without T2DM. However, in those with T2DM, the moderate-fat diet resulted in greater triglyceride reduction (24.8 mg/dL, P < 0.05) than seen with the low-fat diet.26
- Alcohol abuse may be associated with hypertriglyceridemia; nearly 1 in 5 hospitalized alcoholics have triglyceride levels exceeding 250 mg/dL.27 Therefore, in subjects with very high triglyceride levels, complete abstinence is strongly recommended.28
- In a study of 2906 middle aged men, moderately intensive activity (i.e., jogging 10 miles weekly) versus no activity was associated with a 20% lower fasting triglyceride level; the highest activity level (20 miles weekly) was also accompanied by the lowest mean fasting triglyceride level (86 mg/dL).29

7. Pharmacological treatment of hypertriglyceridemia

7.1. Statins

Statins are widely used for lipid lowering as well as CVD risk management. In diabetes, statins are indicated for all patients of CVD and primary prevention of CVD in patients > 40 years with one other CV risk factor (hypertension, albuminuria, etc) irrespective of lipid profile.24 Statins also lower TG levels and increase HDL modestly.31 Trials of statin monotherapy found that increased baseline TG levels predicted worse CVD outcomes and that statins reduced CVD better in patients who had high baseline TGs.34 This provides a rationale
for statin therapy in patients with mild to moderate hypertriglyceridemia.

7.2. Fibrates

Fibrates modulate the activity of nuclear receptor PPAR (peroxisome proliferator-activated receptor)-alpha, resulting in increased lipoprotein lipase activity (causing catabolism of TGs in VLDL and chylomicrons), reduced secretion of VLDL, inhibition of Apo CIII expression, and increased production of apolipoproteins Apo AI and Apo AII. Fibrates reduce TGs by 30%–60% and increase HDL by 5%–15%. 15,35 The effect of fibrates on LDL-C levels are varied. In patients with marked hypertriglyceridemia, LDL-C may be unchanged or substantially increased, 16 whereas fibrates usually reduce LDL-C (5%–20%) in individuals with elevated LDL-C and less severe hypertriglyceridemia. In addition, fibrates may reduce the number of small, more dense LDL particles. 17

In the Veterans Affairs HDL Intervention Trial (VAHIT), men with a history of CHD who had low HDL-C (mean of 32 mg/dL) and low LDL-C (mean of 111 mg/dL) were treated with gemfibrozil (n: 1264) or matching placebo (n:1267) and followed for 5 years. 38 In the overall population, gemfibrozil significantly reduced the risk of a CHD event versus placebo by 22% (P = 0.006), and in the subgroup with TG >150 mg/dL the risk reduction was 27% (P < 0.01). The risk reduction with gemfibrozil was greater with increasing tertiles of baseline TG concentrations.

Although results of the individual trials varied for their primary outcomes, post hoc analysis of these trials and a meta-analysis showed that the relative risk reduction for CVD events was statistically significant in patients with atherogenic dyslipidemia (high TGs and/or low HDL-C). 39,40 In Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, 9795 T2DM patients were randomized to fenofibrate or placebo. The follow-up was for 5 years. In the initial analysis, it was observed that fenofibrate did not reduce CVD events in overall population (Hazard ratio [HR] 0.89, 95% CI 0.75–1.05; P = 0.16). While it reduced CVD events by 23% in subgroup of patients who had baseline TG > 200 mg/dL. 41 These results suggest that CV protective effects of fenofibrate are seen in ADD patients with hypertriglyceridemia, specially when TG > 200 mg/dL. Similarly a meta-analysis of 5 large studies, including 4726 patients on fibrates have shown that fibrate therapy reduce CV events by 35% in patients with TG >204 mg/dL and HDL <34 mg/dL.

In the lipid arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the use of fenofibrate plus simvastatin versus simvastatin alone was examined in 5518 patients with type 2 diabetes mellitus who were at high risk for cardiovascular disease. 42 Fenofibrate reduced TG levels versus placebo but did not significantly reduce the primary CHD outcome, the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes (HR 0.92; P 5.32) over the mean follow-up of 4.7 years. In subgroup analysis of patients with baseline TGs in the highest tertile (>204 mg/dL) and baseline HDL-C below the lowest third (<34 mg/dL), the percent reduction in the primary cardiovascular disease end point was 31% (P < 0.03). 43

Though fibrates are far from ideal drugs to manage ADD. It is well-known that they can increase the serum LDL levels significantly in patients with very high TGs (>500 mg/dL) due to increased LDL production from VLDL. This can be harmful for ADD patients where management of LDL is the primary objective in dyslipidemia management. Fibrates are also known to worsen the renal functions especially when patients has established chronic kidney disease (CKD). Diabetes is most common cause of CKD. 46 They also increases the risk of muscle related adverse events specifically rhabdomyolysis. 47

7.3. Niacin

Niacin at doses up to 3 g/d can lower plasma TG levels by 30%–50%, increase levels of HDL-C by 20%–30% and reduce LDL-C by 5%–25%. 46 The mechanisms of action of niacin are complex and include inhibition of hepatocyte diacylglycerol acyltransferase-2, a key enzyme for TG synthesis; accelerated intracellular hepatic Apo B degradation; decreased secretion of VLDL and LDL particles; impairment of the hepatic catabolism of Apo AI (versus Apo AII), which increases HDL half-life and concentrations of Apo AI-containing HDL subfractions; and inhibition of the removal of HDL-Apo AI. Niacin may also increase the vascular endothelial cell reduction–oxidation state, resulting in the inhibition of oxidative stress and vascular inflammatory genes, key cytokines involved in atherosclerosis. Although niacin may decrease free fatty acid mobilization from adipose tissue via the G protein – coupled receptor, this pathway may be only a minor factor in explaining the lipid effects of niacin. 47

Use of niacin in ADD is difficult as it is known to increase blood glucose and worsen glycemic control. Niacin has also failed to provide cardiovascular benefits in recent studies where patients were already on statin therapy. In the AIM-HIGH trial, investigators examined the effects of high-dose extended release niacin added to statin therapy in 3414 patients with heart and vascular disease and with low HDL-C and elevated TG. One third patients in this study had diabetes mellitus at the baseline. However, results from a pre-planned interim analysis suggested a lack of efficacy for niacin, and, in those treated with niacin versus placebo, a slightly greater rate of ischemic stroke. Therefore, the study was stopped after a mean follow-up of 3 years. 48

7.4. Omega-3 fatty acids

Omega-3 fatty acids, mainly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) reduce TG by approximately 20%–55% and lower TG-rich lipoproteins. 49 EPA and DHA doses of at least 2 g/day are required for significant lipid effects. 50

Omega-3 fatty acids reduce hepatic secretion of TG-rich VLDL particles, reduce the TG content of secreted VLDL particles, and increase TG clearance from the blood by lowering the concentration of Apo CIII, an inhibitor of lipoprotein lipase activity. 51 In addition, omega-3 fatty acids containing EPA and DHA increase the rate of conversion of VLDL to LDL particles and reduce the exchange of TG for cholesteryl esters in circulation, which may produce an increase in plasma LDL-C.
levels. However, the overall number of atherogenic particles is typically not increased.\textsuperscript{52}

In JELIS (Japan EPA Lipid Intervention Study),\textsuperscript{53} 18,645 patients (16\% of which were diabetics) with dyslipidemia were randomized to 1.8 g/day EPA or placebo for 4.6 years. The baseline lipid profile was as following: serum TG: 155 mg/dl, LDL: 188 mg/dl, HDL: 60 mg/dl, total cholesterol: 277 mg/dl. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and nonfatal myocardial infarction, and other nonfatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. At the end of study, a significant 19\% risk reduction in primary end point was noticed in patients in EPA group. However, no significant difference in primary endpoint was seen in diabetic subgroup.

In GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico – Prevenzione) study, 11,324 patients surviving recent (<3 months) myocardial infarction (15\% were diabetics at baseline) were randomly assigned supplements of n-3 PUFA (882 mg EPA/DHA daily), vitamin E (300 mg daily), both, or none (control) for 3.5 years. The primary combined efficacy endpoint was death, nonfatal myocardial infarction, and stroke. The baseline lipid profile was as following: serum TG: 162 mg/dl, HDL: 41.5 mg, LDL: 137 mg/dl and total cholesterol 211 mg/dl. In this study, n-3 PUFA supplement reduced primary endpoint by 15\% and CV death by 30%.

8. Emerging therapies for hypertriglyceridemia in diabetes

8.1. Dual PPAR α/γ agonists

PPAR α agonists are already available in the market (fibrates) which reduces serum triglycerides significantly by increasing activity of lipoprotein lipase. Dual PPAR α/γ agonists are newer agents which reduces serum triglycerides by similar mechanism as fibrates, while they also have insulin sensitizing action by PPAR γ agonist action. Their overall actions are summarized in Fig. 2.

As explained earlier, activation of PPAR α results in increased lipoprotein lipase synthesis and activity in capillaries endothelium (causing catabolism of TG in VLDL and chylomicrons), reduced secretion of VLDL, inhibition of Apo CIII expression, and increased production of apolipoproteins Apo AI and Apo AII. The PPAR α/γ dual agonists are noted to reduce triglycerides, raise cardioprotective HDL levels and improve insulin sensitivity.\textsuperscript{54}

At molecular level, PPAR α agonists bind to the lipid binding domain enabling heterodimerisation with a ligand-activated retinoid X-receptor (RXR).\textsuperscript{55} This process triggers a conformational change, leading to the transrepression or transactivation of target genes. During transrepression, the activated PPAR binds to cytokine activated transcription factors, such as nuclear factor kappa B or activator protein-1.\textsuperscript{56} Under normal conditions, these transcription factors induce the synthesis of proteins involved in the inflammatory response. PPARs can inhibit this process by blocking the interaction between activated transcription factors and the promoter region of the target gene, thereby preventing transcription and reducing inflammation. PPAR α agonists have shown to inhibit the IL-1-stimulated release of IL-6 and inflammatory prostaglandins in vascular smooth muscle cells.\textsuperscript{57}

PPAR γ involves in adipocyte proliferation and differentiation and its agonists improve insulin sensitivity by promoting fatty acid storage and inhibiting adipokine synthesis.\textsuperscript{58} PPAR γ is expressed mainly in white and brown adipose tissue, colon, cecum, endothelial cells, vascular smooth muscle cell (VSMC).\textsuperscript{59} Several preclinical studies have shown that PPAR γ ligands have pleiotropic effects of preventing cardiovascular complications. Agonists of PPAR γ possess potent anti-atherogenic and anti-inflammatory activity by inhibiting several inflammatory mediators such as TNF, IL-1, IL-6 and iNOS, and transcription factors such as NF-κB, Egr-1 and

![Fig. 2 – Physiological actions of dual PPAR agonists.](image-url)
Vascular remodeling, which increases the propensity of atherosclerosis, has been shown to be negatively regulated by PPAR γ agonists due to inhibition of VSMC growth and migration. Endothelial dysfunction, a major risk factor of diabetic vascular complications has been noted to be attenuated by PPAR γ ligands due to inhibition of vascular inflammatory processes. Further, PPAR agonists have beneficial effects in ameliorating hypertension through inhibition of Rho-kinase activation, release of nitric oxide, and their direct calcium channel blocking activity.

Looking at their mechanism of actions, PPAR dual agonists appear to be ideal agents for management of ADD as they reduce insulin resistance (a primary factor in the pathogenesis of ADD) and blood glucose levels in addition to hypertriglyceridemia. Though many dual PPAR agonists (muraglitazar, tesaglitazar, etc.) have undergone clinical trials, most have not progressed past Phase III due to unresolved safety concerns. This may be due to imbalance in proportion of PPAR α/γ agonistic actions of these agents. Changing the ratio of PPAR α/γ agonistic actions of such agents can be a future research interest for management of ADD. Recently, one such agent, saroglitazar is approved in India for the treatment of diabetic dyslipidemia and hypertriglyceridemia with Type 2 diabetes mellitus not controlled by statin therapy. In preclinical studies and human clinical trials, saroglitazar has been found to be exceptionally devoid of conventional adverse events of typical PPAR α agonist agents (reduced GFR, increased myopathy with statins and hepatotoxicity) as well as that of PPAR γ agonist agents (pedal edema, weight gain and congestive heart failure). In phase III studies, saroglitazar also reduced serum triglycerides significantly and was as effective as 45 mg/day pioglitazone in reducing glycosylated hemoglobin (HbA1c).

9. Microsomal triglyceride transfer protein (MTTP) inhibitors

The microsomal triglyceride transfer protein (MTP or MTTP) enzyme is necessary for very low density lipoprotein (VLDL) assembly and secretion in the liver. MTTP is a lipid transfer protein localized in the endoplasmic reticulum of hepatocytes and enterocytes, where it initiates the incorporation of lipids into Apo B, acting as a chaperone to assist in Apo B folding. MTTP is necessary for the formation of very low density lipoprotein (VLDL) particles in hepatocytes and chylomicron particles in enterocytes. This inhibits the synthesis of chylomicrons and VLDL. The inhibition of the synthesis of VLDL leads to reduced levels of plasma LDL-C. Thus MTTP inhibitors are effective in reducing serum TGs and LDL both at the same time.

Lomitapide is an MTTP inhibitor which is approved in both US and The European Union (EU) for management of homozygous familial hypercholesterolemia. In clinical studies of 26 weeks, lomitapide reduced serum TG by 45% and LDL by 50% in patients with homozygous familial hypercholesterolemia. It can be given once daily in dose 5–60 mg, without food.

Lomitapide was tested in a dose-escalation study in 6 patients with homozygous FH. All patients were instructed to follow a low-fat diet and after cessation of all other lipid-lowering therapies for 4 weeks, received lomitapide orally for 4 weeks. Dose-dependent reductions in LDL-C and TG levels were observed; those receiving the 1 mg/kg dose effected a significant 51% and 65% decrease in LDL-C and TG levels, respectively. HDL-C and Apo AI levels did not change significantly while apo B levels decreased by 56% at the 1.0 mg/kg dose.

10. DGAT (diacylglycerol acyl transferases) inhibitors

Diacylglycerol acyl transferases (DGATs) are involved in triglyceride synthesis in adipose tissue, the gut and in the liver. DGAT-2 may be one of the mechanisms by which niacin reduces hepatic triglyceride and hence VLDL production and is expressed in liver and adipose tissue. In contrast, DGAT-1 is expressed in the intestine, liver and adipose tissue and data from DGAT-1 deficient mice and with inhibitors shows that it is a mechanism that mediates reduction in triglycerides, hepatic steatosis, obesity and improvement in insulin resistance.

11. Conclusion

Though statins are very useful to reduce CV risk in diabetic patients, significant morbidity and mortality still remain unaddressed. Many other risk factors in including ADD can account for that. Hypertriglyceridermia is a primary abnormality of ADD in diabetic patients. It is also involved in increased CV risk in diabetic patients. Currently many different therapies are available for management of ADD. Newer option like PPAR dual α/γ agonist (e.g. saroglitazar) are keeping a ray of hope that optimizing the control of ADD will improve CV outcome of diabetic patients which may help in enhancing morbidity and mortality benefits in future.

Conflicts of interest

All authors have none to declare.

References


