

# Diabetes, Dyslipidaemia and Atherosclerotic Coronary Artery Disease

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Diabetes mellitus (DM) is as protean a disorder as is atherosclerosis (AS). Neither of them is simple in its genesis but appears to be the outcome of a constant interaction between nature and nurture.

## Vascular Channels and Plasma Lipids

It is well appreciated that the vascular channels are not mere conduit tubes but are components of a tightly organised, highly regulated and closely integrated fibrocellular system. The uniformity of the endothelial lining and non-thrombogenicity of these channels are maintained by various factors [1]. Inhibition of entry of excess cholesterol into the endothelial cells is of paramount significance. Endothelial cell surface presents specific receptors that combine with apoprotein apoB<sub>100</sub>. Low density lipoproteins (LDL) are the molecules containing apoB<sub>100</sub> and carry the highest amount of cholesterol i.e. 50 percent by weight. These LDL molecules attach to endothelial cells through apoB<sub>100</sub> receptors, get internalised and liberate the necessary load of cholesterol which is very vital for the metabolism of such cells [2]. On the other hand, lipoprotein molecules rich in triglycerides (TG), also containing some amount of cholesterol such as very low density lipoprotein (VLDL) and intermediate density lipoprotein (IDL), get access into endothelial cells through another set of receptor systems which are of little consequence in the healthy state [3].

Well regulated cellular cholesterol homeostasis, maintenance of physiological constant of receptor – apoB<sub>100</sub> combination, contact inhibition of adjacent endothelial cells, intact and electrically appropriately charged membrana propria that prevents adherence and insudation of lipids to subendothelial space along with the limited capacity of formed elements of blood to get deposited/attached to the endothelial surface, are the basic physiological mechanisms designed by nature to prevent AS [1, 2, 4]. However, with advancement of age, these homeostatic mechanisms get gradually deficient and AS develops as a part of senescence. When AS affects arteries of vital organs, the condition is termed atherosclerotic vascular disorder (ASVD). Unfortunately, in patients with DM, ASVD of the extramural coronary arteries (CAD), aorta and its major branches including vessels of the limbs as well as arteries of the brain occurs more commonly, with greater severity and wider distribu-

tion and that too at younger age when compared with non-diabetic subjects [5, 6, 7]. Altered metabolic state in patients with DM may be the major factor in enhancing susceptibility to the process of ASVD, most of all CAD.

## Coronary Atherosclerosis in Diabetes Mellitus

The process of AS and its consequence is more evident in DM. At present, ASVD is the most common complication of DM [8]. In the pre-insulin era it accounted for only 16 to 23 percent of all deaths due to DM in the Joslin's Clinic population [9]. Majority of these deaths, particularly in women (14 percent), were due to CAD. Proportion of mortality from ASVD increased following availability of insulin and extension of life-expectancy. Currently, the average annual incidence of CAD has been found to be two to three folds higher amongst patients with DM than non-diabetic subjects [10]. Further, three-fourth of deaths in diabetics of USA is consequent to ASVD [8]. Diabetic subjects of the third world are no exception to this phenomenon. Our own analysis of data over the past three decades indicates progressive increase in the incidence of CAD as the cause of death, although the overall prevalence of CAD (assessed through non-invasive measures) has been observed to be lower as compared to the Western diabetic population [11, 12].

## Pathogenesis

The genesis and progression of atherosclerotic lesions have been observed to be different in diabetics as compared to non-diabetic subjects [13]. Continued and repeated injury to the endothelium followed by deposition of layers of platelet, migration of smooth muscle cells (SMC) and lipid laddening of the latter along with formation of mural thrombi are the usual stages of atherogenesis in any individual. Such lesions not only require repeated injury for development but are potentially reversible (unless complicated). They are nomenclatured as 'Type 1' or 'Rokitasky type' lesion. On the other hand, susceptibility for ASVD is so much greater in DM, that an isolated injury may be sufficient to initiate atherosclerotic lesions. The process involves laying down of monolayer of platelets releasing 'platelet derived growth factor' (PDGF) as well as thromboxane A<sub>2</sub>. Besides, there are other

atherosclerosis promoting factors in circulation like fibrinogen and von Willebrand's factor which not only enhance platelet aggregation but also stimulate SMC migration and proliferation [6, 13]. Glycation of apoproteins, cell membrane proteins and proteins of the membrana propria along with raised quantity of glucosaminoglycans and advanced glycation end products (AGE) in DM enhances LDL, VLDL and remnant particle binding to endothelial cell, in excess of their physiological constant, with inappropriate deposition of circulating lipids and accelerated atherosclerosis [14]. These type of lesions are termed 'Type 2' or 'Virchow's type' [13]. They are neither dependent on repeated stimuli nor overt hyperlipidaemia basically required in non-diabetic subjects. Although these basic differences in pathogenesis are yet to be fully explained, they bear an important role in understanding the natural history of CAD as well as therapeutic interventions for its prevention in patients with DM.

Epidemiological data suggest that hitherto recognised risk factors (RF) for CAD in the general population contribute only 25 percent with regard to its higher incidence in DM [15]. However, at a younger age, abnormalities in the levels of plasma lipids and lipoprotein cholesterol (LPC) are so far the best established RF for development of premature CAD. Observations over the past two decades suggest that the absolute values of circulating cholesterol (TC) and TG can no longer be given the sole importance as RF for development of AS. Relative distribution of cholesterol in different LP molecules may be of even greater importance. While high proportion of cholesterol in LDL(LDL-c) is known to be more atherogenic, raised amounts of cholesterol in high density lipoprotein (HDL-c) has been considered to be protective against CAD in the general population [2].

### Disorders of Lipid Metabolism in Relation to DM

Liver with its enzyme systems, especially hepatic lipoprotein lipase (HPL), plays the key role in synthesis of endogenous TG as well as apoB<sub>100</sub>. TG synthesised is mostly from free fatty-acids (FFA), generated through futile carbohydrate cycles and glycerol coming into circulation after break down of TG in fat cells and at the tissue-capillary endothelial interface. Incorporation of such TG, ApoB<sub>100</sub> along with some amount of cholesterol produced through the HMG-CoA reductase pathway (hepatic), form the VLDL molecule. Both these family of enzymes i.e. HPL and hepatic-HMG-CoA reductase along with lipoprotein lipase (LpL present at the endothelial surface) and hormone-sensitive lipase which hydrolysis TG content of adipocytes to release free fatty acids (FFA) as well as the enzyme lecithin-cholesterol acyl

transferase (L-CAT) that causes esterification of free cholesterol and activates HDL metabolism are all hormone-primed and require insulin as one of the main agents to stimulate their action [2, 16].

ApoB<sub>100</sub> is the specific apoprotein which combines with receptors on endothelial cell surface and holds the key to conversion of VLDL into smaller lipoproteins like LDL and intermediate density lipoprotein (IDL) consequent to release of TG in circulation. In the event of inadequate clearance of TG-rich Lps, as occurs in a diabetic state, obesity and congenital deficiency of LpL or apoB<sub>100</sub> receptor defects, these get entry into endothelial cells through separate receptor systems and cause excess cholesterol deposition in them [3]. Besides, in diabetes, due to the loss of endothelial electrical barrier consequent to glycation of basement membrane proteins, these TG-rich lipoproteins get access to sub-endothelial layers and cause lipid laddening of SMC's - the key to atherogenesis.

The levels and metabolism of plasma lipoproteins in patients with DM depend upon several specific factors such as type of DM, quality of glycaemic control, levels of circulating insulin and degree of insulin resistance as well as basic nutritional status of the individual [13, 14, 16, 17, 18, 19, 20].

(a) *IDDM* : This is a state of both, poor porto-hepatic and circulating insulin levels and leads to compositional modification of lipoproteins which can be atherogenic (Table 1).

**Table 1**  
**Lipid and lipoprotein abnormalities in IDDM**

VLDL (VLDL <sub>1</sub> , VLDL <sub>2</sub> , VLDL <sub>3</sub> )	: Increased.
LDL (including small dense LDL)	: Marginally raised.
HDL	: Low or normal depending on glycaemic status and insulin therapy.
Triglycerides	: Increased.
Cholesterol	: Esterified cholesterol diminished.

This is more so in inadequately treated patients having poor glycaemic control. The VLDL molecules in circulation constitute a family of lipoproteins (VLDL<sub>1</sub>, VLDL<sub>2</sub> & VLDL<sub>3</sub>) depending on the stage of metabolism and consequently the relative distribution of cholesterol, TG and apoproteins in them. These molecules are increased due to raised production by liver from excess supply of glucose and FFA vis a vis slower peripheral clearance by insulin-

dependent LPL. Due to poor L-CAT activity, there is decreased esterification of cholesterol in HDL, VLDL and LDL molecules. Higher concentration of free cholesterol makes VLDL and LDL more atherogenic while 'reverse cholesterol transport' by HDL gets jeopardised. Insulin therapy and normoglycaemia causes reversal of most of these abnormalities.

(b) *NIDDM*: In patients with NIDDM, there is global disorder of LP metabolism and therefore a wider spectrum of dyslipidaemia (Table 2).

**Table 2**  
**Lipid and lipoprotein abnormalities in NIDDM**

VLDL	: More of large VLDL due to poor clearance - more of circulating apoB <sub>100</sub>
IDL and Remnant Particles	: Increased.
LDL	: More of unesterified cholesterol and prolonged half-life; higher quantities of small dense LDL.
HDL	: Low, normal or raised but efficacy suppressed.
Triglycerides	: Increased.
Cholesterol	: May be increased or normal. Free cholesterol : lecithin ratio increased in LP's

There is an increase in small dense LDL i.e. LDL<sub>3</sub> which is highly atherogenic. In patients with poor glycaemic control, there is higher production of TG - rich lipoprotein i.e. VLDL with poor peripheral clearance due to lesser expression of apoB<sub>100</sub> receptors on endothelial cell surface as a part of receptor defect and/or slower recycling phenomena.

Glycated apoproteins of LDL interact with platelet membrane and induce platelet aggregation. Further, glycated apoB<sub>100</sub> has longer interaction with receptors and so prolongs the half-life of LDL in circulation. These molecules when exposed to subendothelial tissue, are readily taken up by SMC and produce accelerated atherogenesis. In contrast to non-diabetic subjects, HDL levels may not be low in patients with NIDDM having fair glycaemic control. In NIDDM, there is good porto-hepatic insulin concentration which keeps the HDL cycle and hepatic enzyme systems active, but the protective action of HDL against CAD, as seen in non-diabetic subjects, is counteracted by the afore discussed inherent defects seen in the diabetic state. Further, there occurs excess lipoprotein oxidation consequent to auto-oxidation of monosaccharides and generation of free radicals - particularly so in patients with uncontrolled hyperglycaemia. The oxidised LDL molecules not

only cause persistent higher levels of cholesterol in circulation but have been found to inhibit endothelium dependent dilation of coronary arteries through platelets, prostaglandin/prostacycline and nitric oxide mechanisms.

(c) *Undernourished Diabetics (UND)* : The diabetic state differentiates UND from their non-diabetic counterparts i.e. adults with protein-energy malnutrition (PEM) in many respects including morbidity, mortality and lipoprotein profile. Cholesterol content in LDL and VLDL are higher as are TG levels, although the absolute values of these lipid parameters are much lower than in well-nourished diabetics (WND). Levels of mean HDL-c is relatively higher in UND irrespective of glycaemic status. Diabetic subjects, as seen in India and possibly other developing societies, have higher levels of TG whether UND or WND when compared with non-diabetic subjects. This profile is more likely to be the true reflection of the nutritional state of patients with DM in developing societies rather than any specific biological alteration, since population studies conducted by us had revealed 'U' shaped distribution of TG levels in higher, middle and lower socio-economic classes (S.E.C.) [21] respectively. While higher TG levels in the lower S.E.C. is most probably due to higher carbohydrate diet, the same in the higher S.E.C. is more likely consequent to Westernised diets compounded with poor peripheral clearance. To further elucidate this apparent peculiarity, the TG levels were correlated with the body mass indices (BMI) of diabetic patients. In the WND group, there was a positive correlation with BMI suggesting higher TG in obese, very likely due to slower utilisation in circulation, while in UND there was no correlation [11]. In view of the generally lower lipid profile vis-a-vis higher HDL-c in the UND as compared to WND, it may be concluded that, this pattern is likely to be one of the mechanisms for lesser prevalence of CAD in the UND.

(d) *Lipoprotein(A)* : Lipoprotein (a) i.e. Lp(a) is a genetically determined lipoprotein which vary in concentration and distribution from one ethnic group to another and is supposed to be an independent RF for CAD [22]. On ultracentrifugation of plasma, it is isolated from the peak between HDL and LDL and compositionally is more akin to the latter. Certain studies suggest that Lp(a) has a reduced capacity to suppress cellular cholesterol synthesis and so higher quantity of Lp(a) can get internalised into endothelial cells through apoB<sub>100</sub> receptors and cause excess cholesterol laddening and promote atherogenesis [18].

The levels of Lp(a) are more or less uniform in both IDDM and NIDDM but are higher in insulin treated IDDM subjects. In diabetic subjects, Lp(a) levels are

not well correlated with the incidence of CAD, so much as in non-diabetic patients with CAD, but has a positive correlation with circulating insulin levels [23]. Further, levels of Lp(a) have been found to be raised in diabetic patients with both micro and macro-proteinuria hinting at its association with generalised vasculopathy in DM [24].

### Summary and Conclusion

Although lactescence of serum was the first noted lipid abnormality in DM [25, 26], reports of normal VLDL levels in the early 50's and great emphasis on cholesterol as the major lipid abnormality involved in the pathogenesis of CAD resulted in pouring in of reports revealing hypercholesterolaemia to be the characteristic abnormality of diabetic state [27, 28]. As a notable difference, Albrink observed higher TG levels to be more common in DM [29]. Our own findings of raised TG levels in DM was attributed to the inherent high carbohydrate diet in our population. By early 80's we had enough published data to emphasise that raised levels of TG and VLDL were most characteristic lipid abnormalities in DM whether WND or UND[19], either before or after glycaemic control irrespective of the mode of treatment[17]. Neither TC, LDL-c nor HDL-c appeared to be of much significance with regard to CAD[17,30]. Concurrently, similar observations were reported by Nikkila[31] and more recently and more categorically by Laakso et al from Finland [32].

Hypertriglyceridaemia, common in all types of DM, is yet to get an independent status of RF for CAD, although several recent studies and multivariate analyses have found it to be so in DM[33,34,35]. Levels of HDL and composition of cholesterol in it has been observed to be altered and its efficacy with regard to 'reverse cholesterol transport' subdued. Near normal levels of LDL-c does not exonerate it from playing an important role in atherogenesis. Higher quantities of small dense LDL, oxidative products of LDL as found in diabetic subjects are much more atherogenic even at low concentrations [36]. The exact role of Lp(a) in promoting CAD in DM is yet to be fully assessed.

Numerous cross-sectional and longitudinal studies including that of Framingham, have established that the risk of CAD is 3 to 5 times higher in men as well as women with DM [15,37]. This increase in incidence cannot be fully explained by the known RF's operating in the general population. It has been established by MRFIT and Nurses Health Studies that at every level of any individual risk factor, diabetic men are over 3 times and women 6 times more prone to develop CAD, suggesting a very special role played by the diabetic state per se[38,39]. As lipids

are basically involved in the process of atherosclerosis, hyperinsulinaemia, insulin resistance or insulinopenia and hyperglycaemia (characteristic of the diabetic state) must be operating by increasing the atherogenic potential of lipoproteins through changes in key enzymes, glycation and excessive lipid peroxidation.

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