LDL-c typically makes up 60-70 % of the total serum cholesterol. LDL is the major atherogenic lipoprotein and has long been identified by NCEP as the primary target of cholesterol lowering therapy. This designation is based on a wide variety of observational and experimental evidence. The induction of hypercholesterolemia is a prerequisite for atherogenesis. In contrast, low LDL-c levels are well tolerated. LDL-c levels as low as 0.65-1.55 mmol/L are physiologically sufficient. The LDL-c concentration in the newborn is approximately 0.78 mmol/L, indicating that such low levels are even safe.

There are three functional pathways of cholesterol transport in plasma: (i) a pathway that delivers dietary cholesterol from the intestine to the liver, (ii) a pathway that delivers cholesterol from the liver to extrahepatic tissues, and (iii) a pathway in which extrahepatic cholesterol is transported back to the liver. The third pathway is often referred to as reverse cholesterol transport.

**ABSTRACT**

Lipids are one of the four basic types of molecules of life and its derivatives serve diverse functions in the body. Generally acclaimed functions of lipids include shock absorption and insulation, and energy storage of the body. Phospholipids and cholesterol form the integral part of cell membrane. In addition cholesterol serves as the precursor for bile salts, male and female sex hormones, vitamin D and adrenocortical hormones. Complex lipids consist of neutral lipid core of cholesterol esters and or triacylglycerol and proteins are the chylomicrons, VLDL, LDL and HDL which serve as the carriers of fats, fatty acids and other lipids in the body.

Complex lipids are tightly controlled in the body. Its dysregulation has been mainly linked to obesity, diabetes and insulin resistance though the issue is yet to be clearly understood. The present review evaluates recent reports in this regards and try to explain the relationship between dyspidemia and insulin resistance.

**Key Words:** Dyslipidemia, Lipids, LDL-c, HDL-c, insulin resistance

**Introduction**

Cholesterol, triglyceride and the plasma lipoproteins that transport them are normal physiological components of plasma. The lipoproteins in plasma are responsible for redistributing cholesterol and triglyceride between tissues in processes that are fundamental to energy metabolism and cell membrane homeostasis.

Plasma lipoproteins are the vehicles by which cholesterol and triglyceride are transported in plasma. About 70% of plasma cholesterol exists as cholesteryl esters. Both cholesteryl esters and triglycerides are insoluble in water and they are solubilised by their inclusion into lipid-protein complexes known as lipoproteins. Plasma total cholesterol is distributed among three major lipoprotein classes: very low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL). Smaller amounts of cholesterol are also contained into minor lipoprotein classes: intermediate density lipoproteins (IDL) and lipoprotein (a) [Lp(a)].

LDL-c typically makes up 60-70 % of the total serum cholesterol. LDL is the major atherogenic lipoprotein and has long been identified by NCEP as the primary target of cholesterol lowering therapy. This designation is based on a wide variety of observational and experimental evidence. The induction of hypercholesterolemia is a prerequisite for atherogenesis. In contrast, low LDL-c levels are well tolerated. LDL-c levels as low as 0.65-1.55 mmol/L are physiologically sufficient. The LDL-c concentration in the newborn is approximately 0.78 mmol/L, indicating that such low levels are even safe.
which suggest that insulin resistance, working through hyperinsulinemia, enhances hepatic VLDL synthesis and contributes to the elevated plasma triglyceride levels observed in normal-weight healthy subjects, obese non-diabetic subjects and type 2 diabetic subjects8.

Most of the studies on insulin resistance were performed on diabetic population. The studies on which non-diabetic people were involved were also performed on obese or overweight subjects. So the prevalence of insulin resistance in the most common metabolic disorders is still an undefined issue. A study was done in Bruneck, Italy in which the prevalence of insulin resistance in subjects with impaired glucose tolerance (IGT), type 2 diabetes (T2DM), dyslipidemia, hyperuricemia and hypertension were assessed. The results showed prevalence of insulin resistance as 65.9% in IGT subjects, 83.9% in T2DM subjects, 53.5% in hypercholesterolemic subjects, 84.2% in hypertryglyceridemia subjects, 88.1% in subjects with low HDL-cholesterol, 62.8% in hyperuricemia subjects and 58.0% in hypertensive subjects. However, in isolated hypercholesterolemia, hypertension and hyperuricemia, prevalence rates of insulin resistance were not higher than that in non-obese normal subjects. The results suggest that in hypertriglyceridemia and a low HDL cholesterol state, insulin resistance is as common as in T2DM whereas it is less frequent in hypercholesterolemia, hyperuricemia, and hypertension9. Average BMI of subjects of that study was 28.0±0.5 kg/m2.

Endogenous hypertriglyceridemia has been shown to be associated with insulin resistance and impairment in glucose tolerance10-11. Moro et al found a very significant correlation between insulin sensitivity and TG levels, this association is also present at normal plasma TG levels12. Some Japanese studies reported that high concentration of TG and low HDL-C characterizes Japanese type 2 diabetic patients with insulin resistance13-15.
There are several studies which show that insulin resistance is also related with low HDL cholesterol and high triglyceride. Triglyceride concentrations were negatively and HDL were positively correlated to insulin mediated glucose disposal; however their study subjects were obese or overweight. Sum et al studied the relationship between hyperinsulinemia and lipids in non-obese subjects. They found that both basal and post glucose challenge insulin levels are higher in non-obese but hyperlipidemic subjects. Similar report was noted by Laws et al.

There is a study on Finish population in which the degree of insulin resistance and some events of intracellular metabolism of glucose were measured in three groups of subjects with normal glucose tolerance: 1) subjects with isolated low HDL cholesterol (n=12), 2) subjects with low HDL cholesterol and high total triglyceride levels (n=10) and 3) control subjects with normolipidemia (n=17). The results showed that the subjects with low HDL levels are insulin resistant independently of triglyceride levels. In these subjects the rates of whole body glucose uptake was attributable to the decrease in glucose non-oxidation (glycogen synthesis, lipid synthesis and anaerobic glycolysis) and glucose oxidation. The subjects of that study had an average BMI of more than 27 kg/m².

The variation in HDL levels is determined by both environmental and genetic factors. Environmental factors such as obesity especially abdominal obesity, and smoking and sedentary lifestyle influence HDL level. In that study the groups with low HDL levels were more insulin resistant than the control group, even after the exclusion of smokers. Hence insulin resistance in the patient groups could not be explained on the basis of smoking alone. BMI and waist-hip ratio, an indicator of intra abdominal obesity, did not differ between the patients and control subjects, which exclude the possibility that obesity or its distribution could have confounding effects on the results. In respect to diet, subjects of all groups were consuming ordinary Finish diet. In addition, all had total cholesterol levels lower than 6.5 mmol/L, which indicate moderate cholesterol and fat intake. Thus it is unlikely that environmental factors could explain the insulin resistance observed in the patients with low HDL cholesterol.

In a large study (3568 subjects) in Singapore, they found isolated low HDL cholesterol could cause insulin resistance only in presence of fasting hypertriglyceridemia. In that study they identified subjects with low HDL cholesterol (<0.9 mmol/L) but having ideal total cholesterol (<5.2 mmol/L). Their findings showed insulin resistance in subjects having fasting triglyceride level>1.71 mmol/L, but there was no insulin resistance in subjects having fasting triglyceride level <1.71 mmol/L. However, the subjects of that study were heterogeneous in terms of BMI, blood pressure and other determinants of insulin resistance.

A study performed by Orchard et al. showed that the higher the insulin or glucose concentration the higher the atherogenic lipids, total cholesterol, LDL-cholesterol and triglycerides and the lower the protective lipoprotein (HDL-cholesterol).

There are some studies performed on a group of Malaysian Malay subjects who were free from T2DM, obesity, hypertension, IGT and IFG (i.e. free from all risk factors of IR) in those studies out of 246 subjects 118 were hyperlipidemic, of them 64 were with hypercholesterolemia, and 42 were with mixed hyperlipidaemia and 12 were with isolated hypertriglyceridemia. Fasting insulin level was high and insulin sensitivity was compromised in all three types of hyperlipidemia. Median fasting insulin level of subjects with isolated hypercholesterolemia was 64 pmol/L, which was 78 pmol/L in subjects with mixed hyperlipidemia and 109 pmol/L in subjects with isolated hypertriglyceridemia which was 34 pmol/L in normolipidemic subjects. The median HOMA%S of subjects in these three groups was
73, 57 and 45, respectively which was as high as 165 in normolipidemic subjects. The mean HOMA-IR of these three groups was 2.25, 3.16 and 4.59 respectively which was only 1.06 in normolipidemic Malay subjects. In all types of hyperlipidemia, there was lowering of insulin sensitivity24-27. The study reports showed that any derangement in blood lipids causes IR. That finding was very important because they used a population which was free from all risk factors of IR.

It is obvious from the above discussion that insulin and lipids have a close relationship and abnormality of one is followed by abnormality of the other. The issue is that which one follows whom? Whether dyslipidemia starts first which causes IR or insulin resistance starts first and gives rise to derangements in blood lipids. What was the cause behind this correlation?

There are two hypotheses answering this question. It is possible that plasma triglyceride-rich lipoproteins may influence early steps in the insulin action pathway such as insulin binding or early post binding intracellular events consequent on insulin binding. As impairment of insulin action has been reported after an infusion of intralipid. In another hypothesis it is possible that insulin resistance may cause increased triglyceride concentrations. The main triglyceride bearing lipoprotein, VLDL, is primarily produced in the liver and is metabolized in plasma in a delipidation cascade catalyzed by lipoprotein lipase. Interaction of insulin resistance with triglyceride metabolism could be either with lipoprotein lipase activity or with VLDL secretion15. Bidhan et al28 and Schmidt et al29 commented that the lipid pattern of high TG and low HDL-C is a feature of inflammation and they argued that it is due to this and related inflammatory cytokines the insulin resistance results.

Further studies in people with different lipid derangements and insulin resistance are needed with study at molecular level to establish 'cause and effect' relationship between IR and lipid disorders.

References


