REVIEW ARTICLE

Dyslipidemia in Insulin Resistance: Cause or Effect

AK Al-Mahmood[1], SF Afrin[1], N Hoque[2]

[1]*Dept of Biochemistry, Ibn Sina Medical College, Dhaka*
[2]*Dept of Biochemistry, Faridpur Medical College, Faridpur*

ABSTRACT

Lipids are of 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[1]. 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[2-3].

Hyperlipidemia and dyslipidemia: definition and classification

Abnormalities in plasma lipoprotein transport are expressed as either hyperlipidemia or dyslipidemia. The term hyperlipidemia refers to an increase in concentration of one or more plasma or serum lipids, usually cholesterol and triglycerides and the term dyslipidemia is used for either an increase or decrease in concentration of one or more plasma or serum lipids. The relevance of both in atherosclerosis is illustrated by increasing evidence that deficiency of HDL may be as important a risk factor for coronary heart disease as is an excess of LDL[4]. Hyperlipidemia can be classified based on therapeutic considerations as follows:

Table -I: Classification of hyperlipidemia[5]

Type of dyslipidemia	Lipoproteins Involved	Affected Serum Lipids
I. Hypercholesterolemia	LDL	Cholesterol
II. Mixed hyperlipidemia	LDL + VLDL	Cholesterol and triglyceride
III. Hypertriglyceridemia	VLDL	Triglyceride

The desirable lipid profile is as follows: Total cholesterol <5.2 mmol/L, LDL <2.6 mmol/L, HDL $\geqq 1.15$ mmol/L, and triglyceride <1.71 mmol/L. A subject is considered dyslipidemic when one of the above values is affected[1, 6].

Interaction between insulin sensitivity and hyperlipidemia

Derangements in lipid metabolism is a driving force in the pathogenesis of insulin resistance (IR)[7]. The characteristic lipid profile in an individual with insulin resistance includes: (1) decreased serum HDL cholesterol; (2) increased serum VLDL; and (3) less commonly, an increase in LDL cholestero[l8]. The plasma VLDL concentration is determined by two factors: (1) the rate of VLDL synthesis by the liver; and (2) the rate of VLDL removal by peripheral tissues. The former, in turn, is regulated by the ambient plasma insulin concentration and substrate availability. There is much evidence 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 subjects[8].

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 hypertension[9]. Average BMI of subjects of that study was 28.0 ± 0.5 kg/m^2.

Endogenous hypertriglyceridemia has been shown to be associated with insulin resistance and impairment in glucose tolerance[10-11]. Moro et al found a very significant correlation between insulin sensitivity and TG levels, this association is also present at normal plasma TG levels[12]. Some Japanese studies reported that high concentration of TG and low HDL-C characterizes Japanese type 2 diabetic patients with insulin resistance[13-15].

There are several studies which show that insulin resistance is also related with low HDL cholesterol and high triglyceride[16,17]. 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[18]. 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[19].

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[20]. The subjects of that study had an average BMI of more than 27 kg/m^2.

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[21]. 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[22] 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)[23]. 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 ρmol/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 normolipdemic 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 sensitivity[24-27]. 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 secretion[15]. Bidhan et al[28] and Schmidt et al[29] 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

1. National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation and treatment of High Blood Cholesterol in Adults (Adult treatment panel III): Executive summary of the third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and treatment of High Blood Cholesterol in Adults (Adult treatment panel III). **Circulation** 2002; 106.
2. Small DM. The HDL system: A short review of structure and metabolism. **Atherosclerosis Rev** 1987; **16:** 1
3. Rye K-A, Clay MA, Barter PJ. 'Overview of plasma lipid transport' in Barter PJ and Rye K-A eds. Plasma lipids and their role in disease. 1st edition. Harwood academic publishers, Singapore, 1999.
4. Thompson GR. Abnormalities of plasma lipoprotein transport. In: Plasma lipids and their role in disease. Barter PJ and Rye K-A eds. Harwood academic publishers, Singapore: 1999.
5. Ministry of Health, Malaysia. Malaysian Guidelines for Good Clinical Practice, 1999.
6. American Diabetes Association (ADA). Management of dyslipidaemia in adults. **Diabetes care** 2002; **25**: S74-S77.
7. Doherty RO, Stein D, Foley J. Insulin resistance. **Diabetologia** 1997; **40:** B10-B15
8. Defronzo RA, Ferrannini E. Insulin resistance a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. **Diabetes Care** 1991; **14:** 173-94.
9. Bonora E. Prevalence of insulin resistance in metabolic disorders: The Bruneck study. **Diabetes** 1988; **47:** 1643-49.
10. Steiner G, Morita S and Vranic M. Resistance to insulin but not to glucagons in lean human hypertriglyceridaemic. **Diabetes** 1980; **29:** 899-905.
11. McKane WR, Stevens AB, Woods R, Andrews WJ, Henry RW, Bell PM. The assessment of hepatic and peripheral insulin sensitivity in hypertriglyceridemia. **Meatbolism** 1990; **39:** 1240-45.

12. Moro E, Gallina P, Pais M, Cazzolato G, Alessandrini P, Bittolo-Bon G. Hypertriglyceridemia is associated with increased insulin resistance in subjects with normal glucose tolerance: evaluation in a large cohort of subjects assessed with the 1999 World Health Organization criteria of classification of diabetes. **Metabolism** 2003; **52:** 616-9.

13. Taniguchi A, Fukushima M, Sakai M, Kataoka K, Miwa K, Nagata I. Insulin sensitive and insulin-resistant variants in non-obese Japanese type 2 diabetic patients. **Diabetes Care** 1999; **22:** 2100-2101.

14. Taniguchi A, Fukushima M, Sakai M, Kataoka K, Nagata I, Doi K. The role of the body mass index and triglyceride levels in identifying insulin-sensitive and insulin-resistant variants in Japanese non-insulin-dependant diabetic patients. **Metabolism** 2000; **49:** 1001-05.

15. Taniguchi A, Fukushima M, Sakai M, Miwa K, Makita T, Nagata I. Remnant-like particle cholesterol, triglycerides and insulin resistance in non-obese Japanese type 2 diabetic patients. **Diabetes Care** 2000; **23:** 1766-1769.

16. Abott WGH, Lillioja S, Young AA, Zawadzki JK, Yki-Jarvinen H, Christin L, Howard BV. Relationships between plasma lipoprotein concentrations and insulin action in an obese hyperinsulinemic population. **Diabetes** 1989; **36:** 897-904.

17. Zavaroni I, Dall'Aglio E, Alpi O et al. Evidence for an independant relationship between plasma insulin and concentration of high density lipoprotein cholesterol and triglyceride. **Atherosclerosis** 1985; **55:** 259-66

18. Sum CF, Wang KW, Tan CE, Fok Kc, Chew LS and Tan YT. Hyperinsulinemia in non-obese subjects with hypertriglyceridemia: a preliminary report. **Ann Acad Med Singapore** 1992; **21:** 10-13.

19. Laws A, Stefanick ML and Reaven GM. Insulin resistance and hypertriglyceridemia in non-diabetic relatives of patients with noninsulin-dependant diabetes mellitus. **J Clin Endocrinol Metab** 1989; **69:** 343-47.

20. Karhapaa P, Malkki M and Laakso M. Isolated low HDL Cholesterol: An Insulin-Resistant state. **Diabetes** 1994; **43:** 411-417.

21. Tai ES, Emmanuel SC, Chew SK, Tan BY and Tan CE (1999). Isolated low HDL cholesterol: an-insulin-resistant state only in the presence of fasting hypertriglyceridemia. **Diabetes** 1999; **48:** 1088-1092.

22. Orchard TJ, Becker DJ, Bates M, Kuller LH and Drash AL. Plasma insulin and lipoprotein concentrations: an atherogenic association? **Am J Epidemiol** 1983; **118:** 326-337.

23. Al-Mahmood AK, Ismail AA, Rashid FA, Wan Bebakar WM. Insulin sensitivity of non-obese non-diabetic Malay subjects: relationship with lipid status. **Internation Med J** 2006: **13:** 47-52.

24. Al-Mahmood AK, Ismail AA, Rashid FA, Wan Bebakar WM. Insulin sensitivity and secretory status of a healthy Malay population. **Malays J Med Sci** 2006; **13:** 37-44.

25. Al-Mahmood AK, Ismail AA, Rashid F, Mohamed W. Isolated hypertriglyceridemia: an insulin-resistant state with or without low HDL cholesterol. **J Atheroscler Thromb** 2006; **13:** 143-8.

26. Al-Mahmood AK, Ismail AA, Rashid FA, Wan Bebakar WM. Mixed hyperlipidemia in non-obese Malay subjects: relationship with insulin sensitivity. **NCD Malaysia** 2005; **4:** 13-18.

27. Al-Mahmood AK, Ismail AA, Rashid FA, Wan Bebakar WM, Azwany YN. Isolated hypercholesterolemia: its relationship with insulin sensitivity. **NCD Malaysia** 2005: **4:** 22-26.

28. Bidan CS, Hasi RS, AK Azad, Niranjan KS, Subhagata C. Serum Lipid Profile status of Type 2 Diabetic Patients in the cross section population in Dhaka City of Bangladesh. **Bang J Med Sci** 2012; **11:** 121-125.

29. Schmidt MI, Duncan BB, Sharrett AR, Lindberg G, Savage PJ, Offenbacher S. Markers of inflammation and prediction of diabetes mellitus in adults (atherosclerosis risk in community study): a cohort study. **Lancet** 1999; **353:** 1649-52.