Atherosclerosis and diabetes mellitus

Aspects of dyslipidaemia in diabetes mellitus

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Dyslipidaemia in diabetes was referred to by Joslin as early as 1927 and has been the subject of numerous articles. Very often little attention is paid to dyslipidaemia, which plays a major role in the premature development of atherosclerosis in diabetes. It is now increasingly recognised that diabetes is not only a disorder of carbohydrate metabolism but also of lipid and protein metabolism, and attention should be given to these other metabolic aspects and not only the glycaemic control of the diabetic patient.

This article is not intended to be exhaustive, but aims rather to focus attention on the importance of dyslipidaemia in the management of diabetic patients. An overview is given of some of the pathophysiological processes that lead to dyslipidaemia in diabetes, the changes in lipids and lipoproteins that are seen are briefly described, and an outline of the management is presented.

Pathophysiological processes that lead to dyslipidaemia in diabetes

Numerous changes that may lead to dyslipidaemia occur in diabetes (Table I), and these may be present in combination, or may arise when the patient is already diabetic or poorly controlled; others, however, may arise before the patient is overtly diabetic when he/she only has impaired glucose tolerance. A lack of insulin action characterises diabetes but the mechanism by which this lack of insulin action arises in the two major types of diabetes differs, viz., a lack of insulin production in insulin-dependent diabetes mellitus (IDDM) and a resistance to the action of insulin, primarily at post-receptor level, in non-insulin-dependent diabetes mellitus (NIDDM); it is this difference that underlies the differences in the lipoprotein and lipid profiles seen in these two forms of diabetes.

Lipoprotein lipase (LPL). LPL is the key enzyme involved in the catabolism of triglyceride (TG)-rich lipoprotein particles of intestinal and hepatic origin, namely chylomicrons and very-low-density lipoprotein (VLDL) respectively, which leads to the formation of relatively TG-rich remnants, also referred to as chylomicron remnants and intermediate-density lipoproteins (IDLs) respectively. These are subsequently cleared from the circulation by their respective ApoE binding receptors or, in the case ofIDL, further metabolised to low-density lipoprotein (LDL). LPL is an endothelially located insulin-dependent enzyme; with reduced insulin action there is consequently a reduced catabolism of the TG-rich particles such as chylomicrons and VLDL, which leads to an accumulation of their remnants which in turn results in an increase in serum TG. When the deficiency in insulin action is severe this can lead to 'diabetic lipaemia' or a chylomicronaemia syndrome. There is an established inverse relationship between TG and HDL, and HDL is consequently reduced. The activity of the insulin-dependent hepatic triglyceride lipase, which is involved with the further metabolism of the remnants, is also reduced and contributes to the impaired remnant clearance. The reduced activity of these lipases also leads to a relative TG enrichment of LDL. The accumulation of TG-rich particles and the TG enrichment of LDL have both been shown to be associated with increased atherogenicity.

Increased VLDL secretion by the liver. In diabetes an increased secretion of VLDL by the liver has been demonstrated; this contributes to the increase in serum TG. On the one hand, this may be a result of the increased flux of non-esterified fatty acids from the periphery to the liver due to a loss of the peripheral antilipolytic action of insulin. On the other hand the increased VLDL secretion has been associated with the hyperinsulinism seen with insulin resistance, and these increased insulin levels have in the past, quite wrongly, been directly implicated in the increased VLDL secretion. However, insulin has clearly been shown to have an inhibitory effect on VLDL secretion. Furthermore, microsomal transfer protein, the protein involved in the addition of lipids to ApoB and the assembly of VLDL prior to secretion by the liver, is negatively controlled by insulin. The increased VLDL secretion is therefore a further manifestation of the intra-hepatic lack of insulin action; the hyperinsulinism should be seen as a compensatory response to insulin resistance and loss of insulin action, and does not lead directly to the increased VLDL secretion.

Impaired reverse cholesterol ester transport. There is an impaired transfer of esterified cholesterol from HDL to VLDL (reverse cholesterol transport) despite the normal activity of lecithin cholesterol acyltransferase; this leads to an altered lipid content of these particles, which is most probably the result of an increased cholesterol content in the
VLDL and LDL of diabetics. Similar changes have been found in other conditions where there is a high risk for CAD.

**LDL clearance.** LDL particles are formed by the progressive metabolism and TG removal from VLDL and IDL, which leads to a cholesterol-rich particle that is then cleared from the circulation by the LDL receptor or pathologically deposited in peripheral tissues. Binding of LDL to the LDL receptor and subsequent internalisation are partially regulated by insulin, and a decreased clearance of LDL at the level of the LDL receptor has been demonstrated in diabetes. However, a markedly increased serum LDL cholesterol (LDL-C) level is not a common feature in diabetics because the effect of the reduced clearance of LDL particles is, to a degree, offset by the reduced production of LDL particles as a result of the impaired metabolism of VLDL and IDL.

**Glycosylation.** As with other proteins, apoproteins are prone to glycosylation in diabetics, with a resultant impairment of their normal functions. Glycosylation of ApoB, the receptor-binding moiety of LDL, interferes with LDL clearance. LDL also reacts with tissue-derived advanced glycation end-products and this process is worsened with renal impairment, where there is reduced clearance of these products. Glycosylation of LDL further enhances and accelerates the uptake of LDL by macrophages via the 'scavenger' receptors, and part of this accelerated uptake may be due to the enhanced ability of glycosylated LDL to be oxidised. Glycosylation of collagen leads to products that have an enhanced ability to trap LDL and aggravate lipid accumulation in peripheral tissues. ApoE glycosylation interferes with its binding to the LDL receptor and subsequent internalisation are partially regulated by insulin, and a decreased clearance of LDL at the level of the LDL receptor has been demonstrated in diabetes. However, a markedly increased serum LDL cholesterol (LDL-C) level is not a common feature in diabetics because the effect of the reduced clearance of LDL particles is, to a degree, offset by the reduced production of LDL particles as a result of the impaired metabolism of VLDL and IDL.

**Oxidation.** Of late, much attention has been given to the oxidation of lipoproteins in the genesis of atherosclerosis. LDL is only taken up by the 'scavenger receptors' of macrophages after modification, usually by oxidation. Furthermore, these scavenger receptors are not downregulated, which leads to the progressive lipid accumulation in macrophages and formation of foam cells. Oxidation of LDL therefore stimulates the progression of atherosclerosis and also stimulates the release of chemotactic factors that attract macrophages to areas of lipid accumulation. The small dense LDL particles that accumulate in insulin resistance are even more prone to oxidation, which thus increases the tendency to atherosclerosis, despite relatively normal levels of LDL-C. ApoB is also more prone to oxidation in diabetic than in non-diabetic patients.

**Other genetic factors.** Diabetic patients, although they inherit certain genes that predispose them to diabetes, are not impervious to the other genetic influences that determine abnormal lipid profiles in the general population. The distribution of different ApoE phenotypes, which significantly influence variability of cholesterol concentrations in the general population, is no different in diabetics than the general population. Other non-diabetic factors, either genetic or environmental, affect the background lipid profile of a diabetic patient and this background is further modified by the diabetic state. Furthermore, the gene or genes that cause insulin resistance in type II diabetes are also likely to affect the lipid profile directly. The lipid profile in type II diabetes is therefore not solely the result of hyperglycaemia, poor control or the diabetic state.

### The lipid profile in diabetes mellitus

The lipid profile in diabetes is complex and modified by various factors such as the presence of insulin resistance, degree of glycaemic control and the interaction of the genotype with various environmental influences.

**The lipid profile in IDDM.** The lipid profile in IDDM (type I) is, for the most part, dependent on the degree of control of the diabetes and the dosage of insulin. In contrast to NIDDM, the processes that lead to the diabetes are independent of lipoprotein metabolism and do not influence the lipid profile. In the uncontrolled state high TG and lower HDL levels are found, but these may vary from an extreme situation such as a chylomicronaemia syndrome to values that appear entirely normal. This predisposition to develop the chylomicronaemia syndrome may itself be associated with other genetic factors, of which an ApoE2 homozygosity is but one example.

Almost all studies have shown relatively normal or even increased HDL levels when treatment is optimal and stabilised. Mild increases in total cholesterol (TC) and LDL-C levels are occasionally seen but for the most part the lipid profile in optimally controlled IDDM tends to be normal and any residual abnormalities may well be a reflection of the background lipidogenic genetic and environmental influences of that particular population. The improvements in the lipid profile after glycaemic control are the highest for TG and TC, with lesser changes in HDL. The gender differences in cardiovascular disease mortality usually seen in non-diabetics are reduced.
in IDDM and abnormalities in the lipid profile are more pronounced in women with IDDM than in men. The lipid profile is further worsened by the presence of renal disease, which is one of the major determinants of dyslipidaemia in NIDDM. Furthermore, micro-albuminuria is predictive of the later development of dyslipidaemia and cardiovascular complications.

Apart from the quantitative changes described above, certain qualitative and compositional changes occur that may account for some of the atherogenicity of the lipoproteins, despite relatively normal circulating levels of TC. High free cholesterol/lecithin ratios are seen in VLDL and LDL, which may interfere with lipid transfer and reverse cholesterol transfer, including the ability of HDL to accept cholesterol from peripheral cells. Furthermore, these changes do not fully return to normal after optimisation of treatment. Small dense LDL is also increased in IDDM but not to the same degree as in NIDDM.

The lipid profile in NIDDM. Lipid abnormalities are more common in NIDDM (type II) than in IDDM and the underlying genetic factors that predispose to the development of insulin resistance and NIDDM also directly influence lipoprotein metabolism and the lipid profile. Much attention has been given to the coexistence of a complex of abnormalities that largely determines the lipid profile in type II diabetic patients, viz. insulin resistance, hyperinsulinaemia, central obesity, hypertension, dyslipidaemia with high TG and low HDL, hyperuricaemia, increased plasminogen activator inhibitor levels, hyperfibrinogenaemia and a marked propensity to develop atherosclerosis and coronary heart disease, also referred to as the insulin resistance syndrome, syndrome X or the plurimetabolic syndrome. The lipid profile and factors that lead to atherogenesis in the insulin resistance syndrome are complex, occur early and are present before the appearance of overt diabetes. Further, these changes do not fully return to normal after optimisation of treatment. Small dense LDL is also increased in IDDM but not to the same degree as in NIDDM.

Although the LDL-C is not greatly increased in diabetics, the relationship between cholesterol and cardiovascular disease is still present and the rates of CVD are three times higher in those with NIDDM than in non-diabetics. It would therefore be reasonable to assume that quantitative changes in lipoproteins are not the only explanation for the increase in CVD in diabetes. Qualitative rather than quantitative changes in lipids may well play a major role in the development of atherosclerosis in patients with diabetes. In IDDM renal disease is the major determinant of cardiovascular disease and as proteinuria is associated with dyslipidaemia it is reasonable to assume that dyslipidaemia plays a role in the development of atherosclerosis. However, the excess cardiovascular mortality in diabetics is not entirely explained by the lipid profile, and other factors are probably operative.

Management of dyslipidaemia in diabetes

The measures to be instituted should aim to improve glycaemic control as well as improve the lipid profile. Many guidelines for the management of dyslipidaemia have been published, among them the NCEP guidelines. Goals for the treatment of dyslipidaemia usually differentiate between men and women. Because the dyslipidaemia, as well as the mortality and morbidity from cardiovascular disease in diabetes, is the same for men and women, the same goals should apply for both.

All the general non-pharmacological principles of management of dyslipidaemia apply in diabetics. No large-scale prospective study has demonstrated that these measures are effective in reducing the incidence of macrovascular disease but there is every reason to believe that these measures are effective and have the same benefits as in non-diabetics. Furthermore, non-pharmacological measures are highly cost-effective.

Lifestyle modification. In smokers HDL-C is reduced, the susceptibility to oxidation of LDL is increased, insulin resistance is increased and the incidence of hypertension is increased. There is every reason to believe that these parameters will improve with the cessation of smoking. These patients should be enrolled into an active programme with the necessary support if there is to be any hope of success with this measure, and admonition on its own is usually ineffective. Increased physical exercise should be encouraged as this will be beneficial to glycaemic control, obesity and the lipid profile.

Are lipids the explanation for the increased atherosclerosis in diabetics?

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Diet. There is no role for high-fat diets in diabetes, and a low-fat diet comprising less than 30% of calorie intake as proposed by the NCEP is recommended. A high carbohydrate intake also improves insulin sensitivity. An increase in mono-unsaturated fat as provided in olive oil, peanut oil and canola oil is recommended as this has been shown to have a LDL-C-lowering effect. Although omega-3 fatty acids can lower TG levels and improve platelet aggregation, they can raise LDL-C and are not recommended as a routine. A high-fibre diet is not recommended because of the possibility of worsening of renal function.

Glycaemic control. Because of the link between glycaemic control and dyslipidaemia, optimal control of the diabetes is the aim. Sulfonylureas can improve glucose tolerance but may be linked to reduced HDL as well as increased TG and cholesterol, which may be due partially to the weight gain associated with these drugs. Metformin may have independent lipid-lowering (TC and TG) effects and these effects are most marked when the TG level is high. Although there are theoretical objections to the use of insulin in NIDDM because of the possible deleterious effects of hyperinsulinism, these have not been substantiated, and insulin therapy should not be withheld from NIDDM patients for fear of accelerating atherosclerosis. Overnight insulinisation when VLDL production is at its highest may well be beneficial to the lipid profile. However, many of the beneficial effects of insulin may be offset by the weight gain seen with insulin therapy. A new group of anti-diabetic drugs, the thiazolidinediones, improve insulin resistance and troglitazone improves TC, TG and HDL values as well as reducing blood pressure in treated diabetic patients.

Lipid-lowering drugs. Drugs to lower lipids should only be used when the above measures have failed. However, these drugs should not be withheld because, as is often the case, an abnormal lipid profile is found and attributed to poor control. Although the degree of dyslipidaemia is related to poor glycaemic control, an abnormal lipid profile is part and parcel of the disease process in NIDDM and insulin resistance. Bile acid resins are not recommended because they can dramatically increase the TG levels in patients with hypertriglyceridaemia. The gastro-intestinal side-effects are particularly troublesome in the presence of autonomic neuropathy and poor compliance makes these drugs extremely cost-ineffective. Nicotinic acid would appear to be an ideal drug because it reduces TG and TC, and increases HDL: it does, however, aggravate insulin resistance and glucose intolerance and increases uric acid levels, and is therefore not recommended. Fibrates are the drugs of choice as they reduce TG and raise HDL levels. Bezafibrate improves insulin resistance but whether this applies to this group of drugs as a whole is uncertain. The effect of fibrates on fatal and non-fatal cardiovascular events remains to be ascertained and there are some data to suggest that the use of these drugs, notably clofibrate, increases non-cardiovascular mortality. The HMG-CoA reductase inhibitors or statins — simvastatin, pravastatin, fluvastatin — are safe in the treatment of dyslipidaemia of diabetes and mainly reduce LDL-C with minor reductions in TG, although atorvastatin has been shown to reduce TG rather dramatically. The statins furthermore do not adversely affect insulin resistance. The statins also dramatically reduce fatal and non-fatal cardiovascular events during treatment without increasing non-cardiovascular or total mortality. A sub-analysis of the 45 and WOSCOPS studies (secondary and primary prevention, respectively) shows that these benefits extend to diabetic patients and that these effects may be more pronounced in women than men. These drugs are recommended when fibrates have failed and, in fact, replace the fibrates as first choice once more data become available.

Conclusion

Dyslipidaemia in diabetes should not be regarded merely as the result of poor glycaemic control, but deserves rigorous attention in its own right. Diligent efforts to optimise glycaemic control and improve the abnormal lipid profile, as well as attention to the other risk factors for atherosclerosis, e.g. obesity and hypertension, are required if an improved long-term outcome in patients with diabetes is to be realised.

REFERENCES

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