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# Nutritional Management of Cardiac Risk Factors in Type 2 Diabetes

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## INTRODUCTION

In people with diabetes three out of four deaths are caused by cardiovascular disease (1). There is a three- to fivefold increase in myocardial infarction (MI), with an increase up to 10–15-fold once diabetic neuropathy develops. Angina and left ventricular failure are common, while interventions such as angioplasty and coronary artery bypass grafting have worse outcomes in people with diabetes compared with non-diabetic people (2). Thus the management of Type 2 diabetes is largely about addressing cardiovascular risk factors.

The vast majority of people with Type 2 diabetes have associated insulin resistance which is now recognised as the key pathophysiological defect.

## INSULIN RESISTANCE SYNDROME

Reaven, at his Banting Lecture in 1988 (3), first proposed a widespread role for insulin resistance in common diseases such as coronary heart disease, Type 2 diabetes, obesity and hypertension. He proposed an insulin resistance syndrome (IRS) (or Syndrome X) as a unifying theory for a cluster of adverse metabolic changes (Table 9.1). Each of these changes have been independently shown to be related to a risk of cardiovascular disease. Insulin resistance is also a strong marker for the risk of developing Type 2 diabetes and therefore a

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**Table 9.1** Metabolic and related disorders associated with the insulin resistance syndrome

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|---|---|
| Glucose metabolism | Hyperinsulinaemia<br>Glucose intolerance |
| Lipid metabolism | Hypertriacylglycerolaemia (particularly elevation of VLDL-TG and VLDL-apolipoprotein B)<br>Exaggerated postprandial lipaemia<br>Decreased HDL-cholesterol concentrations (particularly $HDL_2$-cholesterol)<br>Preponderance of small dense LDL-cholesterol particles |
| Other | Hypertension<br>Increased coagulation (PAI-1)<br>Central obesity<br>Increased body flux of non-esterified fatty acids (particularly impaired postprandial suppression) |
| Clinical correlates | Cardiovascular disease<br>Type 2 diabetes<br>Gout<br>Breast cancer |

*Source*: Adapted from Reaven (4).

reduction in insulin resistance is a key goal which may delay the onset of Type 2 diabetes. Thus dietary advice to reduce insulin resistance (or increase insulin sensitivity) is essential.

IRS affects lipid metabolism as well as carbohydrate metabolism. Alterations in the lipid profile, as described in Table 9.1, are at the centre of the insulin resistance syndrome (4).

This cluster of risk factors is commonly seen in the presence of obesity, which is thought to contribute to the development of both Type 2 diabetes and increased cardiovascular risk.

In Europe, modest improvements in CHD mortality have occurred during the last two decades (5). It is likely that some of this reduction in CHD mortality is a result of health strategies first introduced in the 1960s that targeted modifiable CHD risk factors. These included discouraging smoking, treating hypertension and lowering cholesterol concentrations. Despite modest falls in the non-diabetic population, no improvement in CHD has occurred within the diabetic population (6).

## *PRESENCE OF INSULIN RESISTANCE BEFORE THE ONSET OF TYPE 2 DIABETES*

It is interesting to note that although the incidence of people with diabetes in the UK is thought to be around 5%, the number of people with insulin

resistance is nearer 25% (7). There are strong genetic determinants for the development of insulin resistance. The offspring of people with Type 2 diabetes have been shown to be more insulin resistant than those with no family history and this relationship is independent of obesity (8). Non-diabetic first-degree relatives of people with Type 2 diabetes also have similar thrombotic risk clustering to their diabetic relatives (9).

In 1990 Haffner *et al.* (10) theorised that macrovascular complications start to develop very early on, initiated by insulin resistance and/or hyperinsulinaemia in the prediabetic state, whereas microvascular complications develop after sustained hyperglycaemia. In the Quebec heart disease study high fasting insulin concentrations were reported to be an independent predictor of ischaemic heart disease in men (11). However, a meta-analysis of a prospective population-based cohort and case-controlled studies, reported by Ruige *et al.* in 1998 (12), found a weak relationship between plasma insulin levels and CVD, suggesting that other risk factors, such as lipids, must also be involved.

## *NOT JUST FASTING LIPIDS BUT POSTPRANDIAL LIPID CONCENTRATIONS*

Only 50% of CHD is explained by traditional risk factors such as smoking, hyperlipidaemia, hypertension and diabetes. This may be because most risk factor assessments and many public health campaigns have focused on fasting lipid levels as their main criteria rather than diets to reduce many of the postprandial metabolic disturbances attributed to insulin resistance. Much of the current work in this area is investigating the role of lipids in the postprandial state.

## *OBESITY AND INSULIN RESISTANCE*

Obesity is the most common condition associated with insulin resistance (13). Obesity is a health problem reaching epidemic proportions in Western countries. In the UK alone some 16% of men and 18% of women are obese (14). Obesity can be defined as a body mass index (BMI) greater than 30 $kg/m^2$. Insulin resistance is frequently observed in obese subjects and constitutes an independent risk factor for the development of Type 2 diabetes and atherosclerosis. The importance of increasing visceral fat (measured by waist:hip ratio) as a risk factor for insulin resistance and cardiovascular disease has also been demonstrated (15).

Weight loss improves insulin sensitivity and any type of therapy, whether it is dietary or pharmacological, that can aid effective weight loss and/or weight maintenance will help prevent some of the deleterious metabolic changes associated with insulin resistance.

### *SUMMARY OF DISTURBANCES AT A CELLULAR LEVEL IN INSULIN RESISTANCE*

At a molecular level cellular factors have been identified that can markedly influence insulin action either directly or indirectly. These include tumour necrosis factor (TNF)$\alpha$, glucose transporters (GLUT) and peroxisome proliferator activated receptor (PPAR)$\gamma$, while increased glucose flux has been shown to induce insulin resistance in skeletal muscle. For a more detailed review see Garvey and Birnbaum (16). There is also likely to be a genetic predisposition to insulin resistance (17).

Current treatments of Type 2 diabetes have little impact on reducing insulin resistance and this may explain why treating diabetes has only marginal benefits on reducing CHD mortality. It is hoped that with the introduction of thiazolidinediones, a novel class of oral agents that reduce insulin resistance, this may change.

Environmental influences on insulin sensitivity are not yet completely understood. Exercise has a strong beneficial effect (18) and obesity a strong adverse effect. The effects of diet on insulin sensitivity are discussed later.

### *DYSLIPIDAEMIC LIPID PROFILE*

Patients with Type 2 diabetes have an abnormal lipid profile with high levels of LDL-cholesterol and triglycerides (TG) and a low level of HDL-cholesterol. Data from the Multiple Risk Factor Intervention Trial (MRFIT) (19) suggest that although levels of total cholesterol and LDL-cholesterol do not differ significantly between patients with and without diabetes, those with diabetes have higher concentrations of atherogenic small dense LDL-cholesterol particles.

A few years ago effects on TG were seen as largely irrelevant, as it was thought that the relationship between TG levels and CHD was weak. However fasting plasma TG concentrations have recently been demonstrated to be an independent risk factor for the development of CHD (20). In a meta-analysis of 17 population-based studies, TG concentrations were particularly important in relation to CHD risk, where a 1 mmol/l increase in plasma TG increased cardiovascular risk by 32% in men and 76% in women.

## DIETARY MANIPULATION

While diet is the mainstay of therapy for people with Type 2 diabetes, the ideal dietary guidelines remain unsettled. Current recommendations aim to promote good glycaemic control and maintain ideal body weight while reducing the risk of CHD through improved lipid profiles. These are very much in line with the

recommendations of the Committee on Medical Aspects of Food (COMA) on diet and cardiovascular disease. In addition to this there is a move away from defined macronutrient prescription and a move towards the treatment of risk factors in the context of lifestyle, behavioural and individualised changes that the patient is willing and able to make. Cultural and ethnic background should be taken into account.

The Stanford group led by Reaven, as well as groups led by Katan, Grundy and Willet have argued for many years that guidelines for CHD and diabetes should be changed from the historic high-carbohydrate/low-fat diet philosophy. They recommend lowering the carbohydrate level and increasing energy from monounsaturated fats which do not demonstrate the postulated detrimental effects of carbohydrate on TG (21).

### *FAT AND INSULIN SENSITIVITY*

Himsworth first made the association between increased dietary fat and insulin resistance in the 1930s and since then much has been published on these effects. In a recently published review on the subject by Storlien *et al.* (22), the premise was developed that the type of fatty acids eaten may be as important as the quantity of fat in the diet. High-fat diets, particularly high saturated fat, are associated with the development of Type 2 diabetes and glucose intolerance, while the intake of long-chain fatty acids, in particular *n*-3 fatty acids, seems protective.

In addition the San Luis Valley Diabetes Study found that high saturated fat and low starch and fibre intakes were associated with hyperinsulinaemia in a non-diabetic population (23).

It has also been demonstrated, using the euglycaemic hyperinsulinaemic clamp method, that increased monounsaturated fat improves insulin sensitivity and glycaemic control while having no adverse effects on lipids (24,25). The mechanism for this is uncertain (26).

### *FAT AND PLASMA LIPIDS*

A high intake of saturated fatty acids has been associated with an increased incidence of CHD, presumably because a high saturated fat intake increases LDL-cholesterol and reduces HDL-cholesterol (27).

The lipid-lowering effects of monounsaturated fatty acids (MUFAs) compared to *n*-6 polyunsaturated fatty acids (PUFAs) are well studied, suggesting that PUFAs may be more potent at lowering plasma LDL-cholesterol and TG (27).

There is accumulating evidence in the literature that increasing the percentage of total energy contribution from MUFA fat has a positive effect on lipids as well as improving glycaemic control in people with Type 2 diabetes.

In a review by Garg (26) monounsaturated fat diets compared to high-carbohydrate diets reduced fasting TG and VLDL-cholesterol by 19% and 22% respectively, with a modest increase in HDL-cholesterol without adversely affecting LDL-cholesterol (25).

### *CARBOHYDRATE AND INSULIN SENSITIVITY*

Daly *et al.* (28) have recently reviewed the evidence and clinical implications of dietary carbohydrates and insulin sensitivity. This is a controversial area. Extensive studies in animals show a detrimental effect of diets very high in fructose or sucrose, particularly in association with induction of hypertriglyceridaemia. The more limited results in human studies show conflicting results, partly because of heterogeneity of design. Certain groups of subjects such as the elderly, sedentary subjects, those with established coronary artery disease, males and hyperinsulinaemic subjects may be more sensitive to very high intakes of sucrose and fructose than others.

### *CARBOHYDRATE AND PLASMA LIPIDS*

The elevation of blood lipid concentrations in response to large amounts of dietary sugars, particularly fructose and sucrose, has been recognised for many years. There are also many other variables that can influence postprandial TG concentrations, such as obesity, excessive alcohol consumption, genetic background and renal failure.

High-carbohydrate diets are reported to increase TG, mainly in short-term studies (29). However, most of these studies have been poorly controlled and have been very short term and thus the evidence is poor. Turley *et al.* (30) recently demonstrated that free-living healthy subjects randomised to a high-carbohydrate diet (59%) had no detrimental effect on fasting TG concentrations over a six-week period.

The literature contains conflicting findings, particularly in studies that contain $>20\%$ of energy from sucrose or $>5\%$ from fructose, where both sugars have been shown to raise TG concentrations. In studies containing amounts of sugars more typical of dietary habits in the Western world, elevated plasma TG concentrations are not usually observed (29). Interestingly, the glycaemic index of carbohydrate was significantly related to serum HDL-cholesterol in a retrospective cross-sectional study of 2200 middle-aged adults, where a low glycaemic diet was the only dietary variable related to the CHD risk factors measured (31).

## OTHER NUTRITIONAL FACTORS ASSOCIATED WITH REDUCED CARDIAC RISK

### *FISH AND OMEGA-3 FATTY ACIDS*

The cardioprotective benefits of the 'Mediterranean' diet and its reduction of mortality are strikingly evident in the results of studies such as the DART study (32) and the Lyon Diet Heart Study (33). The results of these studies are not solely due to the regular inclusion of oily fish, but this did have a key role. Oily fish such as mackerel, herring, sardines, trout and salmon are a rich source of the *n*-3 polyunsaturates. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the long-chain omega-3 PUFAs, are thought to be beneficial due to their anti-thrombolytic and anti-inflammatory action as well as their triglyceride-lowering effects. The UK Department of Health has recommended to the general population that they consume two portions of fish (100 g or 3–4 oz portion) a week, one of which should be oily (34). People with diabetes should be encouraged to include oily fish in the diet, ideally two to three times a week (35). Fish oils are increasingly available in capsule or liquid form. These should provide approximately 0.5–1.0 g of *n*-3 fatty acids per day. Vegetarians, or those allergic to fish, can optimise their *n*-3 intakes by using vegetable *n*-3 sources (rapeseed, canola, linseed and flax oils), but the conversion rate is low and other polyunsaturates can compete.

### *STANOLS AND STEROLS*

Foods enriched with plant stanols and sterols have recently been introduced to the market. Plant sterols and stanols, which are structurally closely related to cholesterol, effectively inhibit the absorption of cholesterol. Plant sterols occur naturally in vegetable oils such as soybean and rapeseed, whereas plant stanols are found in tall oil, a side-product of paper manufacture. Manufactured products containing these products include spreads, cereal bars, cheeses, milk, ice cream and yoghurts. The optimal dose appears to be 1.6–2.0 g/day which equates to $\sim$20 g spread/day. For these products to be effective the recommended intake should be consumed daily. This results in a 9–14% decrease in LDL-cholesterol (36). Moreover, these agents complement the action of the statin drugs, particularly in poor responders to drug therapy who have high rates of cholesterol absorption from the gut but low rates of cholesterol synthesis in the liver. However, concern exists regarding absorption of fat-soluble vitamins. Randomised trials have shown that plant sterols and stanols lower the blood concentration of β-carotene by about 25%, the concentration of α-carotene by about 10% and the concentration of vitamin E by about 8%. However, since these vitamins protect LDL-cholesterol from oxidation and stanols/sterols decrease the amount of LDL-cholesterol, these

changes may self-adjust. Patients should be encouraged to eat foods containing stanols and/or sterols daily to reduce LDL-cholesterol.

### *SOYA PROTEIN, FLAVONOIDS AND PHYTO-OESTROGENS*

The efficacy of soya and soya derivatives in lowering total cholesterol and LDL-cholesterol was recently supported by the US Food and Drug Administration (FDA) approving a health claim about the role of soya protein in reducing the risk of CHD. In 1999 the FDA finalised a rule that authorises the use on food labels and in food packages under FDA jurisdiction of the health claims concerning the association between soya protein and reduced risk of CHD: '*25 g of soya protein a day, as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease*' (37). Serum total cholesterol and LDL-cholesterol concentrations can be lowered by about 13%, plasma TG by 10% and HDL-cholesterol goes up by about 2% (38), and these beneficial effects are also seen in people with Type 2 diabetes (39). It is unclear if the benefits come from the main phyto-oestrogens found in soya, diadzein and genistein or from the soy protein itself. Epidemiological evidence suggests high intakes of flavonols such as onions, broccoli, apples and tea may reduce the risk of CHD or certain cancers – however, as yet, prospective data in disease prevention is lacking.

### *EGGS*

In 2001 the American Heart Association relaxed its recommendations concerning the restriction of eggs and other high-cholesterol foods for the general healthy population, allowing people on plasma cholesterol-lowering diets five to six eggs a week. However, in a recent meta-analysis concern remains in the diabetic population where higher egg consumption was associated with an apparent increased risk of CHD (40). Further research is called for and continuing egg restriction for people with diabetes should be maintained.

### *GARLIC*

Garlic shows some promise for improving some cardiovascular risk factors. Studies suggest small short-term benefits of garlic on some lipid and antiplatelet factors (41). However, conclusions about the true effects of garlic are limited by the marginal quality and short duration of many studies. Debate also continues regarding the quantity of garlic needed to see an effect, with some studies reporting an intake as high as three bulbs per day. The implication for clinical practice is that this may not be the most effective way to reduce lipid levels, but if the patient enjoys garlic then do not dissuade the use of it.

## *HOMOCYSTEINE AND FOLIC ACID*

Elevated plasma homocysteine has been shown in many studies to be an independent marker for an increased risk of cardiovascular disease (42). The mean plasma homocysteine level is usually low or normal in DM patients except when nephropathy is present. Levels in that case tend to be higher than in people without diabetes. For people with diabetes an independent association with homocysteine and CVD has been shown in retrospective studies. Prospective studies showed an association between elevated homocysteine and all-cause mortality in DM patients. In general, the association between elevated levels of homocysteine and an adverse outcome was stronger for people with diabetes compared with non-diabetics.

Homocysteine is formed as a result of the breakdown of the dietary amino acid methionine. This is dependent on the presence of four B vitamins (vitamin $B_{12}$, vitamin $B_6$, folate and riboflavin). Homocysteine reference ranges still need to be clarified, as does the mechanism by which homocysteine damages the vasculature.

To try and prevent a raised homocysteine level, patients should be encouraged to have five portions of fruit and vegetables each day to ensure that adequate amounts of vitamins and minerals are consumed. The combination of vitamins that most effectively lowers homocysteine levels has yet to be discovered. If supplementation with B vitamins is going to form part of a public health strategy to prevent vascular disease, it is important, to avoid toxicity, that the lowest effective dose is found.

In the USA, grain products are fortified with folic acid at a level of 1.4 μg/g of product. Although this is primarily to prevent neural tube defects, it is also hoped that it may be beneficial for vascular disease prevention. Promotion of foods high in the appropriate B vitamins should therefore be encouraged within a healthy diet. There continues to be doubt as to whether supplementation should be encouraged until further research has been completed, and specific information on target groups such as people with diabetes is lacking.

## *COFFEE*

The evidence remains ambiguous regarding the effect of coffee on CHD (43). The association between CHD and coffee consumption has been weakened by long-term follow-up. These findings may possibly be explained by a change in the type of coffee consumed. A lipid-rich fraction from boiled coffee seems to increase serum cholesterol concentration. When boiled coffee is filtered the lipid-rich factor is retained in the filter paper and the effect on cholesterol is reduced substantially (44).

An elevated plasma concentration of total homocysteine is considered to be a risk factor for cardiovascular disease. Heavy coffee drinking has been related to high homocysteine concentrations in epidemiologic studies and one experiment in which healthy subjects drank unfiltered boiled coffee (45).

### *VITAMIN E*

Several observational studies have suggested that a high intake of vitamin E may slow the development and progression of atherosclerosis. Some clinical trials have also reported beneficial effects of vitamin E supplementation in the secondary prevention of cardiovascular events. However, the results of a recent large, multi-centre clinical trial reported that vitamin E supplementation was not effective in reducing the incidence of cardiovascular events in high-risk patients (46).

### *CHROMIUM*

Within the past five years chromium has been shown to improve glucose and related variables in subjects with glucose intolerance and Type 1, Type 2, gestational and steroid-induced diabetes. Chromium is an essential nutrient involved in the metabolism of glucose, insulin and blood lipids. In some studies a suboptimal dietary intake of chromium is associated with increased risk factors associated with diabetes and cardiovascular diseases (47). Minerals such as magnesium, calcium, potassium, zinc and vanadium also appear to have associations with insulin resistance or its management. It is interesting to note that high fibre and wholegrain intakes are also associated with increased intakes of these nutrients in the diet, and this may go some way to explaining the improvements in glycaemic control seen on this type of diet.

Additional studies are urgently needed to elucidate the mechanism of action of these trace elements and their role in the prevention and control of diabetes. However, until this time the benefit from chromium supplementation in diabetic individuals has not been conclusively demonstrated.

## SUMMARY

The balance of evidence suggests that dietary fats, particularly saturated fat, are likely to reduce insulin sensitivity but the effects of dietary carbohydrates on insulin sensitivity are more controversial.

The lipid-lowering effects of MUFAs compared to *n*-6 PUFAs are well studied, suggesting that MUFAs may be more potent at lowering plasma LDL-cholesterol and TG, whereas saturated fat increases LDL-cholesterol. There is

concern that an intake above 55% from carbohydrate exaggerates the postprandial TG response.

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