



Insulin resistance, diet and cardiovascular disease: A review

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Abstract

Obesity and cardiovascular disease (CVD) are two of the leading causes of morbidity and mortality in developed countries. Direct influences of diet on obesity are obvious, however equally strong is the evidence that CVD is caused by and preventable by diet. A common link between these two conditions is insulin resistance (IR), characterised by elevated insulin levels due to an insensitivity to insulin's action postprandially. Recent research has highlighted the strong connection between IR and incidence and severity of CVD. IR is associated with the generation of very small dense low density lipoprotein (LDL) which confers a high risk for cardiovascular disease, more so than any previously identified risk factor for CVD. Given the clear correlation with IR, dietary approaches may be considered to be highly effective as a treatment strategy or preventative measure. This review concentrates on this newly discovered link between IR and CVD, and presents a balanced view of dietary measures which could contribute to corrections in insulin imbalances, responsiveness to insulin, and therefore reduce CVD incidence and obesity.

Key words: Cardiovascular disease, obesity, insulin resistance, diet.

Introduction

Obesity is a well-recognised problem in modern western society and is associated with increased risk of a number of chronic diseases including diabetes, hypertension and cardiovascular disease (CVD)¹. Further, accumulation of fat in the abdominal region particularly increases risk of obesity related diseases. This is of primary concern as the prevalence of such diseases is increasing dramatically, and CVD is the single most common cause of death in developed countries.

Insulin and CVD

There are a number of risk factors for CVD, including lack of physical exercise, smoking and consumption of saturated or oxidized polyunsaturated fats² of both CVD and obesity. Insulin, released from the cells of the pancreas in response to rising blood glucose levels, acts to facilitate the transport of glucose across cell membranes to clear blood glucose levels. Rapidly absorbed sugars, such as those from refined carbohydrates with a high glycaemic index (GI), are rapidly removed from the circulation under the control of insulin and preferentially enter the lipogenic pathway to be stored as fats when glycogen stores are replete. Insulin also regulates plasma levels of triglycerides in the postprandial period, by reducing the metabolism and release of fats into the blood stream from adipose tissue by inhibiting the action of lipases. This ensures that plasma triglycerides levels are not excessively raised while the newly consumed fats are being absorbed, metabolised and/or stored. Insulin activates adipocyte lipoprotein lipase (LPL), which acts to clear lipids being transported in chylomicrons following absorption. Therefore the action of insulin is very important for regulating blood lipids post-prandially, and any disorders in its action impact plasma concentration of both glucose and fats.

Insulin Resistance

Insulin resistance is caused by a relative insensitivity of target tissues to insulin, which may be caused by a number of defects in the insulin signalling pathway, including decreased binding to insulin receptors or defective post-receptor signalling³. The pancreas responds by producing elevated levels of insulin in

order to obtain an adequate response, resulting in hyperinsulinemia. Basal levels of insulin rise with age but are also significantly elevated in obese subjects, and in particular in subjects with abdominal (visceral) obesity⁴. The insensitivity of adipose cells and other target tissues to insulin results in dysregulation of enzymes such as lipoprotein lipase⁵, resulting in elevated and extended postprandial lipaemia due to the failure to rapidly clear plasma triglycerides.

Lipids and CVD

Elevated circulating lipids are a risk factor for cardiovascular disease, as they can contribute to and exacerbate the atherosclerotic build up in blood arteries. Atherosclerosis is initiated by injury (e.g. oxidative and/or inflammatory damage) to the endothelial cell lining of the arteries, allowing the attachment or accumulation of cholesterol, which is the basis for atherosclerotic plaques. LDL (low density lipoprotein) cholesterol is readily oxidised by free radicals, which increases its adherence to the artery walls and uptake into the inner layers of the artery wall, the intima, where further oxidation takes place. Oxidized LDL is phagocytosed by infiltrating macrophages, which stimulates their differentiation into foam cells and promotes plaque formation by the release of chemotactic agents, stimulating further macrophage infiltration. This results in the generation of a large plaque, which becomes encapsulated by a fibrous cap, and blood lipids are deposited, further enlarging the blockage. Rupture of atherosclerotic plaques results in thrombus formation and occlusion of the artery lumen, which can cause reduced blood supply to the heart, leading to myocardial infarction. Elevated LDL cholesterol levels are a predictor of elevated CVD risk, and particularly the ratio of LDL or total cholesterol to HDL (high density lipoprotein). HDL is responsible for transporting cholesterol to the liver to be metabolized and is not as important in the pathogenesis of atherosclerosis, as it is less susceptible to oxidation than LDL and less adherent to arterial endothelial cells. Further, HDL is extremely protective against CVD. Recent epidemiological and prospective studies, such as the Quebec Cardiovascular Study, have described heterogeneity in the size

and type of LDL and the implications for predicting CVD risk⁶.
7. In particular, the presence of very low density small LDL appears to increase risk of CVD three-fold, independent of other risk factors such as triglyceride levels and total cholesterol levels. Small dense LDL are produced by an elevation in the triglyceride content of the LDL, which occurs in the presence of elevated plasma triglycerides⁸, such as those seen in insulin resistance. Triglyceride rich LDL is acted on by hepatic lipases in the liver, which produce the small dense LDL. Due to its smaller size and increased adhesiveness to the extracellular matrix of the endothelium, small dense LDL has higher affinity for the intima of the artery and is more readily oxidised, accelerating the formation of atherosclerotic plaques. Oxidation of the small dense LDL may further promote arterial blockage by promoting activation of prothrombin and other procoagulant factors⁹. This elevation in small dense LDL, which frequently occurs in the absence of elevated total cholesterol levels, is a key element in the syndrome known as atherogenic lipoprotein phenotype (ALP) and is also associated with elevated triglycerides, reduced HDL and elevated serum lipoproteins A and B (protein constituents of LDL)¹⁰. The pathogenesis of ALP is very strongly correlated to, and is likely to be caused by, obesity and insulin resistance. This explains, at least in part, the major problem of CVD in patients with type II diabetes¹¹.

Insulin Resistance and Evolution

From an evolutionary perspective, predisposition to insulin resistance would have been beneficial, in order to cope with cycles of feast and famine. This was recently reviewed by Brand-Miller and Colagiuri¹². Insulin resistance protects the brain and placenta in an environment characterised by low carbohydrate, intermittent high protein, high physical activity – i.e. our evolutionary origins. As a consequence, insulin resistance promotes fat storage during times of high carbohydrate intake, ensuring that energy demands can be met in times of food shortage. With the onset of the agricultural revolution food not only became more plentiful, but the balance of macronutrients altered from a low carbohydrate / high protein diet to a carbohydrate rich diet. Further, the refinement of carbohydrates by removal of fibre and production of ground wheat flour has produced carbohydrates that are more readily digested and absorbed and therefore stimulate a more rapid and amplified insulin response. It is easy to see how in these modern times of plentiful, energy-rich foods, and high intake of refined, rapidly absorbed, high GI carbohydrates, this evolutionary measure to promote fat storage has led to rising obesity and exacerbated insulin resistance. This theory is reinforced by the sharp increase in type II diabetes with the introduction to Britain in the 17th century of refined flour and potatoes and the prevalence of such conditions in populations that have more recently adopted a western diet and lifestyle, such as the Australian Aborigines¹².

Dietary Strategies

To reduce serum cholesterol levels to the normal range, therapeutic low saturated fat, low cholesterol diets are recommended for patients at risk from coronary heart disease. However, the recent association between insulin resistance and CVD may lead to a number of different dietary strategies. Conventional low fat/low cholesterol diets tend to be rich in carbohydrates, leading to elevated blood glucose levels which may exacerbate symptoms of insulin resistance. The key to reducing CVD risk and obesity, which can predispose to insulin

resistance, is to use dietary approaches to reduce circulating insulin levels or improve the insulin – glucose uptake mechanism, to restore the balance in blood triglycerides, cholesterol and glucose levels.

Lowering the intake of carbohydrates or altering the balance of macronutrients can have significant effects on parameters of ALP. A further dietary approach is to not only adjust the total intake of carbohydrates, but to emphasize carbohydrates which have a reduced impact on blood sugar levels and therefore on insulin production. Low glycaemic index carbohydrates are more slowly digested and absorbed, leading to a controlled rise in blood glucose levels. This results in a reduced insulin response, as lower concentrations of insulin are required to bring blood glucose levels back to basal levels. The glycaemic index of a carbohydrate food source is determined by the balance of different starches (amylose, amylopectin, resistant starch) and the amount of proteins, fats, and soluble and insoluble fibre present. Digestion is slowed down by the presence of both soluble and insoluble fibre, such as from grains and fruit, which reduces the speed of glucose absorption from the intestine by increasing intra-luminal viscosity. Proteins and fats are slower to digest than carbohydrates and therefore have a similar effect in reducing glucose absorption if consumed as a constituent, or with, carbohydrate sources. Preferential consumption of carbohydrates with a low glycaemic index accompanied by sufficient protein and fibre, reduces serum glucose and insulin levels, which in turn has beneficial effects on plasma LDL and triglyceride levels¹³. Additionally, ensuring adequate intake of dietary micronutrients that are essential for insulin action (e.g. chromium) or glucose and fatty acid metabolism (e.g. vitamins B1, B2, B3 and B6) is essential for correct energy utilization / storage. In addition to their actions on slowing glucose entry into the blood, dietary protein, fats and fibre have been shown to have independent actions on blood lipid and cholesterol levels. Increased fibre intake improves the ratio of HDL to total cholesterol by the preferential reduction of LDL levels^{13,15}. Similarly, elevated intake of vegetable protein (both wheat- and soy- derived) has been demonstrated to decrease the ratio of total cholesterol to HDL by decreasing LDL concentrations, decrease the proportion of oxidized LDL and reduce levels of serum triglycerides^{14,17}. This beneficial effect may be in part attributable to soy-derived isoflavones and wheat-derived phenolics exerting direct effects on cardiovascular tissues. These recent data suggest that increased intake of protein from vegetable sources and fibre can assist in restoration of normal serum triglycerides and lipoproteins.

Beneficial Effects of Lipids

Previous studies have shown that substitution of monounsaturated fat (e.g. oleic acid) for carbohydrate reduces triglyceride levels and improves glycaemic control¹⁸. Mono- and poly-unsaturated fatty acids from plant oils also have well-promoted roles in increasing HDL, which again affects the ratio of LDL to HDL. These data suggest that the currently recommended therapeutic diet could be modified to emphasize fats from vegetable sources, to increase the effectiveness of correcting blood lipid / cholesterol profiles and reducing insulin levels. This is supported by a trial conducted by Dumesnil and colleagues¹⁹ where a low fat / low GI carbohydrate-rich diet, with a high intake of protein not only reduced plasma triglyceride levels, but also had other beneficial effects - lower

cholesterol and increased diameter of LDL particles. Furthermore, energy intake was significantly reduced on the modified diet, which would assist in weight management. Several recent clinical trials have investigated the effect of essential fatty acids on the serum cholesterol and lipid levels. Supplementation with omega 3 series fatty acids derived from fish oils was shown to significantly reduce plasma triglyceride levels^{20,22} and attenuate the postprandial lipid response, resulting in a reduction in the proportion of small dense LDL. One possible mechanism is through the stimulation of LPL in adipose tissue, leading to rapid clearance of newly absorbed fats from the circulation²⁰. Omega 3 fatty acids may have further beneficial effects with respect to cardiovascular health due to the anti-thrombotic influence through the production of thromboxanes with low blood clotting potential.

Other Considerations

A number of micronutrient imbalances may also be directly associated with CHD risk, independent of the effects of insulin resistance. An example of this is the recently discovered link between raised homocysteine levels and mortality from CHD (reviewed^{23,24}). Homocysteine is an intermediate product during the enzymatic conversion of the amino acid methionine to cysteine. Elevated levels of homocysteine have been shown to be pro-oxidative and it has been proposed that these may increase oxidative damage to vascular endothelium and therefore increase the likelihood of oxidised LDL accumulation and plaque formation. Generally homocysteine levels are low, due to its efficient conversion to cysteine or back to methionine, but these processes are dependent on vitamins B6, B12 and folic acid. Deficiencies in any or all of these micronutrients may therefore increase the damage to the cardiovascular system and predispose to heart disease, especially when dietary protein is high. Similarly, deficiencies in nutrients essential for normal functioning of the heart or blood vessels, such as calcium, magnesium and potassium may have detrimental effects on cardiovascular health. Finally, as the initial step in atherosclerotic plaque formation is oxidative damage to the endothelium, reducing the oxidative status of blood vessels by enhancing intrinsic antioxidant systems would reduce the risk of plaque build-up. Plant foods contain a wide range of phytochemicals, including the flavonoids, isoflavones and carotenoids, all of which exhibit potent antioxidant effects, as do vitamins A, C and E, acting locally to terminate the chain reaction of free radical damage in blood vessels and other tissues. A well balanced, varied, diet rich in sources of these micronutrients and phytochemicals would therefore assist in maintenance of cardiovascular health.

Conclusions

In summary, a number of previously unknown risk factors for CHD and agents involved in the pathogenesis of atherosclerosis have recently come to light and these mean that a number of novel dietary strategies may be used to lower risk of CHD and associated mortality. The description of the atherogenic lipid phenotype and its close association with insulin resistance and type II diabetes highlights the need for alteration of the conventional low fat therapeutic diet for CHD, which may exacerbate this condition by emphasizing intake of carbohydrates. Lowering insulin levels and thereby correcting imbalances in circulating glucose and fat concentrations is also

the key to successful weight loss. It is clear that any dietary strategy to improve cardiovascular health would aim to readjust the imbalances in blood lipid profiles, reduce the oxidative potential of LDL and improve responsiveness to insulin.

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