

openheart Added sugars drive coronary heart disease via insulin resistance and hyperinsulinaemia: a new paradigm

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'I know of no single acceptable study that shows a high intake of sugar in a population that is almost entirely free from heart disease.'¹—John Yudkin

Coronary heart disease (CHD) is responsible for one in every six deaths in the USA,² and it eventually manifests as an acute myocardial infarction (MI). In the USA, almost 1 million acute MIs occur each year² with approximately 15% of patients dying as a result of their acute event.² If one manages to survive an acute MI, depending on the age of onset, the average survival time ranges anywhere from just 3.2 years to up to 17 years.² Thus, CHD and acute MI are leading causes of early mortality in the USA.²

Asymptomatic hyperglycaemia is a risk factor for cardiovascular disease (CVD) and CHD, as well as death from CHD.³ Hyperglycaemia can develop during an acute MI, even in patients without diabetes,³ which may be caused by an increase in catecholamines, a reduction in the release of insulin, development of insulin resistance and increases in cortisol and growth hormone.³⁻⁵ However, many patients with MI already have diabetes and simply have yet to be diagnosed (ie, latent diabetes), where the acute stress worsens their diabetic state leading to hyperglycaemia.³ Indeed, one study showed that 73% of patients presenting with an acute MI have abnormal glucose tolerance, with 50% having diabetes.⁶ After 6 months, 43% still had abnormal glucose tolerance, which is approximately threefold higher than that found in matched controls (15%), the difference between the two being significant.⁶ Thus, hyperglycaemia does not seem to be an acute or temporary finding in patients who have experienced an MI, with many of these patients having continued abnormal glucose tolerance even when followed for several years after their event.

The Whitehall study, a prospective cohort study encompassing 18 403 patients, showed that blood glucose after a 2-hour oral glucose

tolerance test was related to the age-adjusted CHD mortality after 7.5 years.⁷ In non-diabetics, a 2-hour blood glucose at 96 mg/dL or higher was associated with a twofold increased risk of CHD mortality.⁷ An elevated insulin response to an oral glucose load has been found in patients with atherosclerosis of the peripheral, cerebral and coronary arteries.^{8,9} In the Busselton, Australia study, insulin levels 1 hour after ingesting a 50 g oral glucose load were significantly related to the 6-year CVD incidence and 12-year CVD mortality in men aged 60 and older.¹⁰ In both the Helsinki policeman study¹¹ and the Paris civil servant study,¹² insulin levels taken in the fasting state after an oral glucose load (75 or 90 g) were associated with the occurrence of MI and CHD death 5 years later in men aged 30–59. However, the insulin:glucose ratio had the closest association with CVD. In all three studies, the relationship of insulin with CVD was independent of other covariates, including lipids, blood pressure and blood sugar.¹³ Considering that refined sugar, even when compared with starch, has been found to raise serum insulin levels,^{14,15} this provides compelling evidence that overconsuming added sugars (sucrose or high-fructose corn syrup) may lead to an increased risk of CHD through raised insulin levels.

The evidence incriminating insulin and carbohydrate in atherogenesis is strong, and that this scheme would link atherosclerosis with diabetes, obesity, hyperlipaemia, lack of physical exercise, and, possibly, hypertension.¹⁶ (Stout and Valance-Owen)

It has been known for over 50 years that people with hypercholesterolaemia and hyperlipaemia generally have abnormal carbohydrate metabolism, with an elevated insulin level often driving their hyperlipidaemia.¹⁷ Indeed, insulin has been found to increase lipogenesis¹⁸ and stimulate smooth muscle cell proliferation.¹⁹⁻²¹



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Hyperinsulinaemia is also an independent risk factor for CHD,^{10 11} and insulin resistance predicts future cardiovascular risk.^{22 23} Increased levels of insulin are found in multiple disease states, including obesity, coronary artery disease, hypertension, peripheral vascular disease and those with hypertriglyceridaemia.²⁴ Thus, any dietary factor that worsens glucose tolerance or promotes insulin resistance will also likely increase the risk of acute MI, CHD and CHD mortality. Considering that a diet high in added sugars (particularly the fructose component) leads to insulin resistance,^{25–28} the overconsumption of added sugars is undoubtedly a contributing factor to CHD and CVD mortality. Indeed, compared with a diet that contains less than 10% of calories from added sugars, a diet containing 25% or more calories from added sugars nearly triples the risk for CVD mortality.²⁹

Data from animal and human studies have noted that the isocaloric replacement of starch, glucose or a combination of both, with sucrose or fructose, increases fasting insulin levels,^{14 15} reduces insulin sensitivity,^{25–27} increases fasting glucose concentrations,³⁰ increases glucose and insulin responses to a sucrose load^{14 15} and reduces cellular insulin binding.²⁵ In other words, calorie for calorie, consuming added sugars is more harmful than starch or glucose regarding worsening of insulin sensitivity and glucose tolerance. Additionally, feeding rats sucrose leads to impaired glucose tolerance³¹ and adipose tissue that is less sensitive to the effects of insulin.^{32 33} Thus, data from animals and humans indicate that overconsuming added sugars drives insulin resistance and hyperinsulinaemia.

During an acute MI, the heart switches from primarily using fatty acids as energy to using glucose. As insulin facilitates glucose uptake into cells, patients with insulin resistance during an acute MI will have a worse prognosis. Indeed, the degree of insulin resistance is related to the severity of an MI,³⁴ and after an MI diabetics are more likely to die compared with non-diabetics.³⁵ A diet high in added sugars promotes insulin resistance and diabetes,^{14 15 28 36 37} and thus may lead to larger MIs and increase the risk of CHD mortality.

It is well known that those with diabetes have a higher risk of mortality and MI versus those without diabetes,³⁸ which is independent of smoking status, cholesterol levels, blood pressure and body fat distribution. Additionally, patients diagnosed as being newly diabetic also have an increased risk of MI. Diabetics also have more coronary atherosclerosis than non-diabetics,^{39 40} particularly a higher frequency of severe narrowing of the left main coronary artery and healed transmural ventricular scars.⁴¹ The Framingham study showed that those with diabetes have an approximate threefold increased risk of dying from CVD versus the general population as well as an increased risk of stroke, CHD and peripheral arterial disease.⁴² Higher blood pressure or higher lipoproteins did not account entirely for the increased incidence of CHD among diabetics.¹³

A diet high in added sugars has been shown to increase the prevalence of diabetes, whereas a lower intake has

the opposite effect.^{43–46} Thus, added sugars promote an increased risk of CHD by increasing the risk of diabetes, which has been shown in both ecological analyses as well as clinical trial data. Considering that added sugars also promote insulin resistance, and those who experience an acute MI are more likely to be insulin resistant, the overconsumption of added sugars drives CHD.^{25 27}

A raised cholesterol level is not the only risk factor in those with CHD. Indeed, many other abnormalities commonly occur such as elevated glucose, insulin, triglycerides, uric acid and lower levels of high-density lipoprotein cholesterol.⁴⁷ Additionally, impaired glucose tolerance, insulin resistance and altered platelet function are commonly found in patients with CHD or those with risk factors for CHD.^{48–51} All of these CHD abnormalities are induced or worsened in humans and animals when given a diet high in sugar,^{52–55} which can be reversed when reverting back to a diet low in sugar.^{14 55} This provides compelling evidence that the overconsumption of added sugars is a principal driver of CHD.

Administration of a diet high in sugar for just a few weeks leads to approximately one-third of men experiencing numerous changes seen in CHD and peripheral vascular disease.^{53 54} These suggest that the overconsumption of sugar and the subsequent insulin resistance and/or hyperinsulinaemia drive CHD as well as other diseases such as hypertension, diabetes, obesity and gout.^{56 57} Interestingly, smoking, which is a risk factor for heart disease, has been found to induce hyperinsulinism,⁵⁸ suggesting that both the overconsumption of added sugars and smoking predispose to heart disease in a similar manner (via hyperinsulinaemia; although both also induce inflammation, oxidative stress and increased platelet adhesiveness).^{59–61}

Over the past 200 years, the average intake of added sugars has increased from 4 to 120 lb/year.⁶² Sugar is even more rewarding than cocaine in animal studies, and in humans added sugar is arguably the most widely consumed addictive substance around the world.⁶³ The fact that diabetics have an increased risk of occlusive arterial disease,²⁴ and that non-diabetic patients with vascular disease have raised insulin levels,²⁴ suggests that insulin resistance is at the centre of heart disease. Considering a diet high in added sugars can induce insulin resistance and hyperinsulinaemia in humans, and a reduction in added sugars can improve these metabolic derangements, there is compelling evidence that the overconsumption of added sugars (high-fructose corn syrup and sucrose) is a principal driver of CHD. Indeed, refined sugar, as compared with fat, starch, glucose, or a combination of starch and glucose, promotes greater detriments on glucose and insulin levels in humans.^{14 15 28 36 37}

Currently, the main dietary culprit thought to lead to CHD is saturated fat. However, the overconsumption of added sugars (sucrose or table sugar and high-fructose corn syrup) has also been associated with an increased risk of CVD and mortality from cardiovascular causes. A diet high in added sugars for just a few weeks has

been found to produce numerous abnormalities found in patients with CHD including elevated insulin levels and insulin resistance. More importantly, a diet low in added sugars and refined carbohydrates has been found to reverse all of these metabolic defects. The evidence indicates that added sugars are a likely dietary culprit leading to CHD.

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