Under physiological conditions, the human heart derives energy from glucose, fatty acids, and/or lactate depending upon substrate availability, circulating hormone levels, and nutritional status. Circulating free fatty acid and glucose levels often exceed the normal range, as observed with type 2 diabetes, obesity, or physical inactivity. Chronic exposure of the heart to high plasma levels of free fatty acids may cause accumulation of toxic lipid intermediates within cardiomyocytes. Furthermore, suppression of glucose oxidation by increased fatty acid uptake shunts glucose into the oxidative pentose phosphate and hexosamine biosynthetic pathways, both of which yield potentially harmful products. Noxious derivatives of aberrant glucose and fatty acid oxidation can activate signalling cascades leading to myocyte dysfunction or death, processes termed ‘glucotoxicity’ and ‘lipotoxicity’. This review discusses the effects of dietary extremes (e.g. high fat and high carbohydrate consumption) and substrate overabundance in the context of heart failure (HF) development and progression. Emerging data suggest that substrate excess leads to cardiac dysfunction and HF, which may be prevented or slowed by maintaining low body fat and high insulin sensitivity and consuming a diet of low glycaemic load that is high in mono- and polyunsaturated fatty acids.

**KEYWORDS**
Diabetes; Diet; Glucotoxicity; Heart; Lipotoxicity

### 1. Introduction

The constant demand for cardiac mechanical power is supported by a high rate of ATP production fueled by myocardial fat and carbohydrate oxidation. The myocardium adjusts quickly to changes in arterial substrate concentrations, giving it the metabolic flexibility needed for feeding and fasting and variations in food composition. The heart is also built to meet the energy demands of intense exercise, therefore at rest extracting and oxidizing fatty acids and glucose at ~5 to 30% of the maximal capacities for flux. Under healthy conditions, there is little accumulation of intracellular triglyceride (TG) and glycogen despite high rates of fatty acid and glucose uptake. This is attributed to relatively low plasma free fatty acid (FFA) concentrations (~0.8 mM) and tightly-regulated glucose homeostasis (~4–5 mM). However, an elevation in plasma fatty acids, such as with fasting or starvation, accelerates fatty acid uptake and oxidation, inhibits glucose oxidation, and increases myocardial TG and glycogen stores.

Whole body insulin resistance, a hallmark of the metabolic syndrome, obesity, a poor diet, or a sedentary lifestyle, triggers an elevation in plasma FFAs, TGs, glucose, and insulin and presents the myocardium with an overabundance of lipid and carbohydrate substrates. Chronic exposure to excess circulating fuels can have a toxic effect on the heart due to formation of noxious derivatives of glucose and lipid metabolism, such as reactive oxygen species (ROS) from glucose or ceramides from saturated fatty acids. Recent studies where cardiac fatty acid uptake and/or storage were increased in transgenic mice found accumulation of TG and ceramides in cardiomyocytes associated with tissue pathology and deterioration in systolic function. In addition, chronic exposure of the heart to hyperglycaemia or accelerated glucose uptake can increase toxic non-glycolytic metabolism of glucose through the oxidative pentose phosphate or hexosamine biosynthetic pathway. Taken together, this suggests that accumulation of lipid and glucose metabolites in the myocardium could contribute to the development and progression of heart failure (HF), though there is little clinical evidence to support this hypothesis.

Much has been made of the energy-starvation hypothesis, the idea that the failing myocardium is chronically energy deprived. However, most of this literature suggests that energy depletion originates from alterations in phosphate metabolism (e.g. decreased creatine kinase-phosphocreatine...
shuttle activity), ATP transport (e.g. impaired adenine nucleotide translocase function), and/or respiratory chain dysfunction secondary to mitochondrial DNA damage, protein modification/downregulation, and/or cardiolipin depletion. While the capacity for glucose and fatty acid oxidation are both downregulated in severe HF, it is difficult to assess changes in cardiac metabolism due to the increase in circulating fatty acids, glucose, and insulin derived from peripheral metabolic abnormalities in end-stage disease. Thus, maintenance of energy balance and a normal metabolic milieu is required to nourish the myocardium and perhaps slow the progression of HF.

There is a worldwide epidemic in metabolic disorders and heart disease due to obesity, physical inactivity, and over-consumption of diets rich in highly-refined foods. Thus, there is growing interest in understanding the effects of chronic excess of circulating substrates. This review will discuss recent findings on the role of carbohydrate and lipid overabundance, emphasizing the toxic effects of fuel substrates in cardiomyocytes and on the development of cardiac hypertrophy and HF. The contribution of diet to atherosclerosis and coronary disease, which potentially leads to myocardial damage via infarction, has been reviewed elsewhere and will be discussed only as a means of presenting epidemiological evidence relating diet to cardiovascular risk. Our focus here is to illuminate the direct effects of substrate availability and diet on the myocardium independent of coronary heart disease (CHD).

2. Dietary lipid and carbohydrate: new paradigm for prevention of cardiovascular disease?

Diet is a primary determinant of substrate availability, the hormonal milieu, and the development of obesity and insulin resistance. Dietary guidelines for >50 years have recommended consumption of a low saturated fat/high complex carbohydrate diet to reduce the risk for CHD. Since the 1960s, low-fat and reduced-fat food has been marketed, decreasing total fat intake and replacing it with simple carbohydrates largely from highly-processed foods and sugar-sweetened beverages. Concurrent with these modifications was increased prevalence of obesity and type 2 diabetes, both of which are at pandemic proportions and increase the risk for cardiovascular disease.

Recent epidemiological studies show a positive association between dietary carbohydrate consumption and CHD, with reduced risk with high vegetable fat intake (Figure 1). Importantly, eating a diet high in sugar and rapidly-absorbed starch increased the risk for CHD. Regarding fat intake, numerous epidemiological studies have shown that diets low in saturated fat, trans fat, and cholesterol significantly lower risk for CHD. However, in the Women’s Health Initiative, reducing total fat from 37.8% of energy intake at baseline to 28.8% after 6 years of follow-up did not affect the rate of CHD events or stroke compared to no intervention. Furthermore, high carbohydrate diets raise postprandial glycaemia and promote insulin resistance, thereby increasing risk of cardiovascular disease, dyslipidaemia, obesity, and diabetes. Increased fat intake, when coupled with restricted intake of refined carbohydrate, has beneficial effects on weight loss, glycaemic control, lipid profile, and inflammatory markers. Low carbohydrate/high fat diets have also been shown to improve biomarkers of cardiovascular disease in normal weight, normolipidemic subjects independent of weight loss. Based on these and other findings, nutritional guidelines have shifted away from the old diet-CHD paradigm that paid little attention to carbohydrate intake. Current recommendations emphasize increasing consumption of polyunsaturated fatty acids and reducing glycaemic load and total energy intake. Nevertheless, there is limited experimental and clinical evidence examining the role of diet in the pathogenesis of HF. Thus, at present, it is unclear if this new nutritional paradigm will be effective in the treatment of HF. In the following sections, we shall review the effects of diet and substrate overabundance on the myocardium and postulate how they may affect the natural history of HF.

3. Excess lipids and the heart

Plasma fatty acids are the primary carbon fuel for the myocardium but, when elevated, can adversely impact the heart. Early work found a strong association between elevated plasma FFA and ventricular arrhythmias during an

![Figure 1](image-url) Risk for coronary heart disease (CHD) after multivariate adjustment in women according to consumption of macronutrients. Plot displays mean (filled circles) and range of hazard ratio per decile of macronutrient intake. Increased glycaemic load correlated with increased risk for CHD. Greater consumption of vegetable fat significantly reduced risk for CHD, while the level of total fat intake had no effect. Figure drawn from data published in Halton et al.30
acute ischaemic event. More recent studies showed that elevated plasma FFA is a strong predictor of sudden cardiac death in either patients undergoing coronary angiography followed for 7 years or healthy middle-aged men followed for 22 years. This association could be due to deleterious effects on mitochondrial function or activation of Na⁺ or Ca²⁺ channels, thereby triggering ventricular arrhythmias.

The uptake of fatty acids by the heart is primarily determined by the plasma FFA concentration, which is regulated by the rate of lipolysis in adipose tissue. In healthy people, arterial FFA concentration varies ~4-fold in a normal day (~0.2–0.8 mM) but can increase rapidly to >1.0 mM in response to adrenergic stimulation such as with exercise, angina, or emotional stress. FFA levels increase when insulin suppression of lipolysis is low, as with insulin resistance (e.g. obesity, type 2 diabetes, or chronic physical inactivity) or with low insulin levels (starvation, type 1 diabetes, exercise). Regulation of cardiac FFA metabolism is complex (see reviews addressing this topic). Once FFA enter the cytosol, they are esterified to fatty acyl-CoA and converted to TG or to long-chain fatty acyl-carnitine by carnitine palmitoyltransferase-I (CPT-I) (Figure 2A). Approximately 80% of long-chain fatty acids taken up by the heart are immediately oxidized to CO₂ and 20% enter the intracellular TG pool. In healthy people, the myocardial content of TG is low (~3 mg g⁻¹ tissue) relative to the rate of FFA uptake (~3 mg g⁻¹ h⁻¹). Assuming that 20% of the FFA uptake enters the intracellular TG pool, and the mean turnover time is 5 h, illustrating the dynamic nature of intracellular cardiac TG metabolism. Plasma FFA concentration regulates cardiac TG content, as seen in recent NMR spectroscopy in healthy humans, which found a progressive increase in myocardial TG stores with short-term food restriction (70% increase) or starvation (260% increase) corresponding with elevated plasma FFA.

An important effect of elevated plasma FFA on the heart is suppression of glucose and lactate uptake and oxidation through inhibition of phosphofructokinase and pyruvate dehydrogenase activity. Reducing plasma FFA with diet or drugs rapidly decreases myocardial fatty acid oxidation and increases pyruvate oxidation. In addition, high plasma FFA and oxidation by the heart reduce myocardial mechanical efficiency by increasing the energy expenditure for a given rate of contractile power. The mechanism for this effect is unclear but could be due to both mitochondrial uncoupling, accelerated futile cycle flux, or a lower ATP:O ratio for fatty acids than pyruvate.

In addition to these rapid acute effects, more sustained exposure of the heart to high FFA levels will activate peroxisome proliferator-activated receptor α (PPARα) and upregulate the expression of pyruvate dehydrogenase kinase-4, which inhibits the activity of pyruvate dehydrogenase (see Section 3.1 below).

Recently, attention has been placed on lipid accumulation in the heart and the adverse effects on cardiac function and clinical outcome, particularly in diabetic or obese patients. Morbidly obese individuals frequently present with hypertension, left ventricular hypertrophy (LVH), and impaired contractility as a function of obesity duration which might be due to toxic effects of lipid in the myocardium. Septal TG levels, as assessed by magnetic resonance spectroscopy, correlate positively with body mass index. Furthermore, cardiac biopsies from HF patients with obesity or type 2 diabetes have elevated myocardial TGs compared with healthy controls. To date, no evidence provides a causal link between myocardial lipid accumulation and cardiac dysfunction or HF in a clinical population. On the other hand, some non-clinical studies have found evidence for lipid-induced cardiac pathology and HF and suggest several potential mechanisms.

### 3.1 Cellular mechanisms

In the setting of divergent uptake and oxidation, increased exposure of the heart to circulating fatty acids raises the intracellular pool of long-chain fatty acyl-CoA. Accumulation of fatty acyl-CoA provides a substrate for non-oxidative processes, such as triacylglycerol, diacylglycerol, and ceramide synthesis with subsequent cardiomyocyte dysfunction and apoptosis. FFAs also have direct effects on mitochondria, possibly increasing membrane permeability and cytochrome c release. Excess FFAs also can reduce phosphatidylinositol-3-kinase/Akt signalling and activate NF-κB.

Fatty acids modulate cardiac metabolism and mitochondrial function through the PPAR family. PPARα is activated by long-chain fatty acids, eicosanoids, and fibrates, and controls expression of genes involved in fatty acid uptake, esterification, transport into mitochondria, and β-oxidation. Though having a more diffuse expression pattern, PPARβ/δ has been shown to increase palmitate oxidation in neonatal and adult cardiomyocytes and to partially rescue expression of β-oxidation enzymes imposed by PPARα deficiency. PPARγ is highly expressed in adipose tissue, promoting glucose uptake and triglyceride storage, and is the target of the insulin-sensitizing thiazolidinediones used in the treatment of type 2 diabetes. PPARγ indirectly modulates cardiac metabolism through direct effects on circulating fatty acids, adipokines, and insulin sensitivity.

Cardiac-specific overexpression of PPARα results in increased fatty acid oxidation, elevated serum TG, hepatic and cardiac insulin resistance, LVH, and systolic dysfunction which is exacerbated by high fat feeding. These studies suggest that long-term PPARα activation can be deleterious to the heart. On the other hand, pharmacological activation of PPARα in rats with HF had no adverse effects, suggesting that a modest increase in activity is without major functional consequence in chronically stressed myocardium.

The adipose-derived hormone leptin produces satiety and is positively correlated with percentage body fat. Genetic deletion of leptin in rats and mice results in obesity, hyperlipidaemia, cardiac contractile dysfunction, and LV chamber dilation. The leptin deficient obese Zucker diabetic fatty rats develop eccentric LV remodelling and systolic dysfunction with age concomitant with increased myocardial TG content, accumulation of ceramides, and apoptosis compared with normal rats. A similar phenotype is observed in obese leptin deficient ob/ob mice. Due to the obesity, hyperinsulinaemia, and diabetes that develops in leptin-deficient animal models, it is difficult to ascertain...
Figure 2 Schematic depiction of myocardial metabolism under conditions of normal substrate concentrations (A) and elevated fatty acids (B) and glucose (C). GLUT, GLUT1 and GLUT4 glucose transporters; G 6-P, glucose 6-phosphate; PDH, active pyruvate dehydrogenase; TCA cycle, tricarboxylic acid cycle; FATP, fatty acid transport proteins; FFAs, free fatty acids; CPT-I, carnitine palmitoyltransferase-I; ETC, electron transport chain.
whether cardiac dysfunction is mediated directly by myocardial steatosis.\textsuperscript{91} As such, numerous transgenic mouse models have been developed to alter myocardial fatty acid uptake or oxidation independent of body mass or peripheral insulin resistance. Mice with cardiomyocyte-specific overexpression of long-chain acyl-CoA synthetase, an enzyme highly expressed in the heart and responsible for catalyzing the first step in fatty acid metabolism, displayed myocardial neutral lipid droplet formation and increased cytochrome c and ceramide content.\textsuperscript{13} Similar results have been obtained in mice with cardiomyocyte-restricted expression of lipoprotein lipase.\textsuperscript{15} Associated with higher lipase activity was increased heart weight to body weight ratio, LV dilation with systolic dysfunction, and decreased survival. Furthermore, overexpression of fatty acid transport protein-1 produced LV and atrial hypertrophy, diastolic dysfunction, and electrocardiographic abnormalities.\textsuperscript{14}

TG storage in the heart also correlates with lipoprotein synthesis. It has been well-documented that null mutations in apolipoprotein B (apoB) and microsomal triglyceride transfer protein (mtp)–genes involved in lipoprotein assembly and secretion—lead to substantial TG accumulation in hepatocytes and enterocytes.\textsuperscript{92,93} ApoB and MTP are expressed in the heart as well, suggesting that the heart can export surplus lipids.\textsuperscript{94,95} Myocardial TG stores decrease with cardiac-specific expression of human ApoB and increase with MTP knockout.\textsuperscript{96} Lack of lipid accumulation in ApoB-overexpressing mice prevents contractile dysfunction in streptozotocin-induced diabetes.\textsuperscript{97} Similarly, ApoB production reduces lipotoxicity caused by lipoprotein lipase overexpression and molecular markers of HF.\textsuperscript{98}

3.2 Effects of high fat diets on the heart

Transgenic animal models, despite their utility, often represent supraphysiologic conditions that rarely mimic human pathologies. From a clinical perspective, it is more relevant to assess the effects of substrate handling on cardiac function and pathology on a normal genetic background in models of progressive HF. Thus, if lipotoxic cardiomyopathy is an established clinical entity supported by experimental evidence, it should be exacerbated by increased fatty acid availability, such as upon consumption of a high fat diet. However, as will be discussed below, it appears that high fat diets are ‘neutral’ or cardioprotective, especially when high in \(\omega-3\) polyunsaturated fatty acids.

Recent evidence suggests that consumption of a diet rich in vegetable fat, specifically polyunsaturated fatty acids, decreases the risk for CHD (Figure 1). This observation has prompted a paradigm shift in dietary recommendations for prevention of CHD away from low fat/high carbohydrate diets towards greater fat intake.\textsuperscript{16,99,100} However, there is little information regarding the role of fat intake in the development of HF. Epidemiological data show that high intake of \(\omega-3\) polyunsaturated fatty acids from fish is associated with a lower incidence of HF.\textsuperscript{102} A similar benefit was observed in rats with pressure overload-induced LVH and dysfunction,\textsuperscript{102} suggesting that dietary intake of \(\omega-3\) polyunsaturated fatty acids prevents the development of HF. Additional animal studies indicate that a high fat diet comprised of either saturated or unsaturated fatty acids is not deleterious to the heart. Normotensive rats fed a high fat diet (60% total energy from fat) for 8 weeks did not develop LVH compared with a high carbohydrate/low fat diet.\textsuperscript{103} Inhibition of CPT-I increased cardiac TG content but did not lead to systolic dysfunction.\textsuperscript{104} Feeding a high fat diet to hypertensive Dahl salt-sensitive rats attenuated LVH, contractile dysfunction, and LV dilation compared with a high carbohydrate chow.\textsuperscript{105,106}

Hypertension in the Dahl rat is induced by high dietary salt intake\textsuperscript{107} which, subsequently, may alter feeding behaviour and macronutrient intake. Thus, studies have been performed in other models of pressure overload to eliminate the confounding effects of elevated sodium. In a rat model of abdominal aortic banding, a low carbohydrate/high fat diet attenuated LVH and reduced LV remodelling and contractile dysfunction compared with a high carbohydrate/low fat diet.\textsuperscript{108} The lower LV mass with a low carbohydrate/high fat diet was associated with decreased leptin and insulin concentrations, consistent with the idea that these hormones regulate cardiac growth.\textsuperscript{109} Furthermore, LV end-systolic and end-diastolic volumes were inversely correlated with plasma FFA concentration among banded animals. These findings are in agreement with recent epidemiological data (Figure 1), demonstrating that increased fat consumption does not exacerbate the development of CHD. The neutral effects of high fat feeding are not specific to the rat. Mice subjected to transverse aortic constriction (TAC) and a high fat diet (60% energy from fat) showed no difference in body mass, heart weight, plasma TGs, insulin, ventricular architecture, or ejection fraction compared with animals fed a high carbohydrate/low fat diet.\textsuperscript{110} Furthermore, high fat feeding prevented a decrease in both medium-chain acyl-CoA dehydrogenase and citrate synthase activities in animals subjected to TAC, suggesting maintenance of mitochondrial oxidative capacity in the fat-fed animals.

The rat infarct model of HF displays a similar response. A high fat diet had no adverse effects on LV remodelling or systolic function compared with a high carbohydrate/low fat diet despite increases in plasma FFAs, TGs, and leptin in animals subjected to coronary artery ligation.\textsuperscript{54,111} Myocardial TG and ceramide content were both increased but were not associated with worse LV systolic function. In addition, high fat feeding in infarcted animals increased state 3 and state 4 mitochondrial respiration with lipid and non-lipid substrates compared with animals on the high carbohydrate/low fat diet.\textsuperscript{111} Therefore, in this model, it appears that increased exposure to fatty acids had no toxic effects on the heart. Collectively, the pressure overload and infarct studies conflict with data from transgenic models of increased fatty acid uptake and oxidation. Thus, in the context of a normal genetic background, high fat feeding prevents LVH, LV dilation, and contractile dysfunction in rodent models of HF.

4. Glucotoxicity

The toxic effects of glucose overabundance on the heart are not as well-defined as those for fatty acids. Recent data showed that increased fasting plasma glucose is a predictor of hospitalization for HF, suggesting that dysglycaemia may exacerbate HF progression.\textsuperscript{112} Prospective studies link hyperglycaemia to cardiovascular events and poor outcome, as even modest increases in glycosylated
haemoglobin or glycaemia are associated with increased risk of myocardial infarction, angina, and ischaemic heart disease and cardiovascular death. Prolonged insulin resistance and accompanying increases in plasma glucose and insulin concentration may lead to LVH and contribute to the development of HF. While the focus of this review is on the cardiotoxic effects of substrate overabundance, it is important to recognize that activation of cardiac insulin signalling induced by hyperinsulinaemia likely contributes to cardiac hypertrophy and pathology in hypertension or following myocardial infarction.

4.1 Cellular mechanisms
Similar to fatty acids, glucose mediates its toxic effects when there is a disconnect between uptake and oxidation. High sugar intake and/or insulin resistance would overexpose the heart to glucose and chronically activate insulin signalling pathways, which would induce cardiomyocyte protein synthesis and LVH (Figure 2C). Chronic hyperglycaemia increases flux through the hexosamine biosynthetic pathway and N-acetyl-glucosamine production, which induces insulin resistance, cardiomyocyte hypertrophy and apoptosis, myocardial fibrosis, and ROS production.

Another potential mediator of oxidative damage is the oxidative pentose phosphate pathway, of which glucose 6-phosphate dehydrogenase (G6PDH) is a rate-controlling enzyme. Normally, this pathway serves to provide cytosolic NADPH and generate ribose 6-phosphate for de novo purine nucleotide synthesis. However, under hyperglycaemic conditions, glucose flux through this pathway may be increased and fuel paradoxical ROS production via NADPH oxidases and uncoupled nitric oxide synthase. Mice with heart-specific deletion of lipoprotein lipase had increased myocardial glucose oxidation. Conversely, LV homogenates from a canine model of HF or HTV exhibited greater LVH and ventricular remodelling compared with the low carbohydrate/high fat diet.

4.2 Evidence from animal and human studies
Mice with an 80% reduction in G6PDH activity presented with reduced vascular oxidative stress and less atherosclerosis. Aortic tissue from these mice displayed low NADPH concentration and protection against angiotensin-II-induced oxidative stress. Moreover, humans with G6PDH deficiency, the most common enzymopathy in the world, exhibit lower cardiovascular mortality. Conversely, LV homogenates from a canine model of HF or from HF patients who have upregulated G6PDH activity, high levels of NADPH, and increased superoxide levels which are normalized by G6PDH inhibition. Thus, oxidative stress via the pentose phosphate pathway may be a culprit in the severely hypertrophied or failing heart where glucose oxidation is upregulated, particularly if a high carbohydrate/low fat diet is consumed. The exact role of this pathway in the pathogenesis of HF requires further investigation.

Cardiac glucotoxicity could occur under conditions where there is chronically decreased myocardial fatty acid metabolism, resulting in reciprocal acceleration of glucose metabolism. Mice with heart-specific deletion of lipoprotein lipase had increased myocardial glucose oxidation. Associated with increased glucose metabolism was intolerance to pressure overload, increased interstitial and perivascular collagen content, and impaired age-related cardiac function. Similarly, increased cardiomyocyte glucose uptake caused by PPARγ overexpression leads to cardiac hypertrophy, LV dilation, and systolic dysfunction. Additional work is needed to determine if increased glucose flux is responsible for the cardiac pathology observed under these conditions.

Glucose may exert toxic effects through transcriptional regulatory mechanisms. Glycosylation increases the stability of the transcription factor Sp1, which is activated by increased glucose availability and pressure overload and regulates reversion to the fetal isoform programme during cardiac hypertrophy. Thus, increased glucose metabolism indirectly may play a role in molecular alterations associated with HF pathogenesis.

4.3 Effects of high carbohydrate diets on the heart
Recent studies in rats and mice with arterial hypertension suggest that a high carbohydrate diet, particularly one high in sugar, increases the incidence and/or severity of HF compared with a low carbohydrate/high fat diet. Hypertensive Dahl rats fed a high fructose diet (60% energy derived from fructose) had significantly increased mortality (Figure 3), decreased LV hemodynamics, and ejection fraction reduction compared with animals fed a low carbohydrate/high fat diet. Similarly, rats subjected to abdominal aortic banding and fed a high sucrose diet (62% energy from sucrose) exhibited greater LVH and ventricular remodelling compared with the low carbohydrate/high fat group. Multivariable regression analyses indicated that plasma insulin concentration was positively associated with both end-systolic and end-diastolic volumes. Mice subjected to TAC and fed a high fructose diet (61% energy derived from fructose) exhibited significantly increased mortality compared with a high starch diet. Fructose-fed TAC mice had increased end-systolic diameter and decreased ejection fraction compared with sham, effects which were completely prevented with a high starch diet. Interestingly, high fructose decreased the activities of medium-chain acyl-CoA dehydrogenase and citrate synthase and dramatically upregulated mhcβ with TAC compared with animals fed either a high starch or high fat diet (Figure 4). These findings suggest that carbohydrate composition may have an even greater impact than that of fat and concur with evidence linking increased glycaemic load to risk for CHD (Figure 1).

![Figure 3](cumulative_mortality_in_hypertensive_Dahl_salt-sensitive_rats_feed_a_high_fat_60%_total_energy_from_fat_20%_carbohydrate_fat_sugar_complex_carb_fructose). Total cumulative mortality in hypertensive Dahl salt-sensitive rats fed a high fat (fat, 60% total energy from fat, 20% carbohydrate), fat + sugar (45% fat, 25% fructose), complex carb (57% starch, 10% fat), and fructose (52% fructose, 10% fat) for 12 weeks. *P < 0.05 compared with all other diets. Figure drawn from data published in Sharma .
be to (i) maintain low body fat content and high insulin sensitivity through restricted food intake and daily physical activity, (ii) eat a relatively low carbohydrate diet (40–55% of energy intake from carbohydrate) comprised of foods with a low glycaemic index, and (iii) consume fat of vegetable and marine origin that is rich in mono- and polyunsaturated fatty acids (30 to 40% of energy intake). Clearly, extensive interventional studies are needed before incorporating this strategy into clinical dietary guidelines.

7. Conclusion

There is strong evidence that substrate overabundance contributes to the development and progression of HF. The myocardium can adapt to these metabolic changes but may lose this flexibility with continued stress. With the worldwide epidemic in metabolic disorders and resultant heart disease, additional emphasis should be placed on preventing substrate excess through weight control, physical exercise, and proper diet. Emerging data suggest that HF may be prevented or slowed by maintaining low body fat and high insulin sensitivity and consuming a diet of low glycaemic load that is high in mono- and polyunsaturated fatty acids.

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References


71. Kong JY, Rabkin SW. Palmitate-induced cardiac apoptosis is mediated through CPT-1 but not influenced by glucose and insulin. J Biol Chem 2002;277:49676–49684.


