Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease[1−3]

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ABSTRACT

Currently, we are experiencing an epidemic of cardiorenal disease characterized by increasing rates of obesity, hypertension, the metabolic syndrome, type 2 diabetes, and kidney disease. Whereas excessive caloric intake and physical inactivity are likely important factors driving the obesity epidemic, it is important to consider additional mechanisms. We revisit an old hypothesis that sugar, particularly excessive fructose intake, has a critical role in the epidemic of cardiorenal disease. We also present evidence that the unique ability of fructose to induce an increase in uric acid may be a major mechanism by which fructose can cause cardiorenal disease. Finally, we suggest that high intakes of fructose in African Americans may explain their greater predisposition to develop cardiorenal disease, and we provide a list of testable predictions to evaluate this hypothesis.   *Am J Clin Nutr* 2007;86:899–906.

KEY WORDS   Fructose, uric acid, sugar, arteriosclerosis, endothelial dysfunction, hypertension, obesity, chronic kidney disease, metabolic syndrome

INTRODUCTION

Despite our best efforts, the epidemic of cardiorenal disease continues to increase at an alarming rate. Obesity affects one-third of adults and one-sixth of children in the United States and continues to increase; although dietary interventions are often initially successful, they often fail over time because of attrition (1). Likewise, hypertension affects nearly one-third of the population, but despite the presence of effective antihypertensive agents, nearly two-thirds of these patients remain either untreated or are treated ineffectively (2). Furthermore, even if the hypertension is controlled, these subjects continue to have increased cardiovascular mortality (3). Diabetes, a complication of obesity, now affects 7% of our population, with approximately one-third doomed to develop various complications such as retinopathy or nephropathy (4). Kidney disease also continues to increase at a deplorable rate, a consequence of the increasing frequency of hypertension and diabetes (5). Today, nearly 20 million Americans have stage 1 kidney disease or greater (defined as the presence of microalbuminuria or a glomerular filtration rate <90 mL·min^{-1}·1.73 m^{-2}; 6), and, although treatments such as angiotensin-converting enzyme inhibitors are beneficial, they act primarily to delay the progression to renal failure as opposed to halting the process (7).

It is our opinion that the potential mechanisms underlying the epidemic should be carefully reappraised. On the basis of both the experimental studies performed in our laboratories and an extensive review of the literature, we revisit an old hypothesis that a simple dietary substance may have a significant role in driving the epidemic. Interestingly, reappraising the role of sugar and its influence in the development of cardiorenal disease may lead to a new understanding of why certain populations, such as African Americans, Native Americans, Maori, and Australian Aborigines, are at greater risk of developing the disease. Similar to the relation between high intakes of salt or protein and the risk of developing kidney disease or to the relation between a high-fat diet and the atherosclerotic phenotype, we propose that sugars containing fructose may play a major role in the development of hypertension, obesity, and the metabolic syndrome and in the subsequent development of kidney disease. Although physical inactivity and overeating are major contributors to the obesity epidemic, we present evidence that fructose may be the "caries" at the epidemic's root.

THE EPIDEMIC OF CARDIORENAL DISEASE

If the goal is to understand the causes of the epidemic, it is important to first review the literature to understand the timing and origins of the epidemic of cardiorenal disease. This type of epidemiologic analysis may provide insights into the potential etiologies that can then be tested in the experimental setting.

After the introduction of the inflatable cuff for blood pressure measurement by Riva Rocci in the late 1800s, population-based studies were performed throughout the world (reviewed in 8). A

study performed between 1907 and 1919 in >140 000 healthy adults applying for life insurance in the New York region suggested that a blood pressure of 140 (systolic)/90 (diastolic) mm Hg was abnormal because it reflected only 5-6% of the population in the United States (9); however, by nature, these early studies may not have been representative of the general population because they usually did not include subjects of lower socioeconomic status who could not afford insurance or patients who had been previously diagnosed with a disease. Nevertheless, on the basis of these early studies, a blood pressure of 140/90 mm Hg was adopted as the definition of hypertension.

There has been a remarkable increase in the prevalence of hypertension in the US population since the early 1900s. In a study performed in 1939 of >11 000 residents in the Chicago area, only 11-13% of the adult population had blood pressures in the hypertensive range (10); this increased to 25% in 1975 (11), to 28% in 1990 (12), and to 31% (61 million people) in 2004 (13).

Similar observations were noted in other countries. Hypertension was initially rare in all parts of the world except in Europe, particularly in England, France, Germany, and the United States (14–16). In studies conducted as late as 1940, hypertension appears to have been almost nonexistent in non-Western peoples, including studies performed in Native Americans, Australian Aborigines, Maori, Alaskan Eskimos, Asians, and African blacks (reviewed in 8). However, with the introduction of a Western culture and diet, there has been a significant change. The prevalence of hypertension has been increasing throughout the world, and the greatest relative increase has been observed in groups with less socioeconomic support (8).

Not surprisingly, a rise in hypertension is paralleled by increasing rates of obesity and diabetes. In a study of Civil War veterans, obesity [defined as a body mass index (BMI; in kg/m^2) >30] was observed in only 3.4% of 50- to 59-y-old male veterans in 1890, but this percentage rose slightly to 5.9% by 1900 (17). Obesity rates continued to increase during the early 1900s, reaching 14.5% in 1976–1980, 22.5% in 1988–1994, and 30.4% in 1999–2002 (4, 18). Similarly, Osler (19) estimated a prevalence of 2–3 cases of diabetes per 100 000 persons in the population in 1893; however, today, type 2 diabetes affects >7% of our population and is estimated to double in prevalence by 2020. The increases in the rates of obesity and diabetes are being observed throughout the world (20). As with hypertension, these conditions are greatest among the less privileged in societies such as African Americans, Native Americans, and Hispanics in the United States; the Maori in New Zealand; and Aborigines in Australia (20).

There has also been a remarkable increase in chronic kidney disease (4, 21). The incidence of end-stage renal disease in the United States has increased 4-fold between 1980 and 2002 (21), and similar increases are being observed throughout the world. Most of the increase is due to diabetes and hypertension. The incidence of end-stage renal disease in the United States has increased 4-fold between 1980 and 2002 (21), and similar increases are being observed throughout the world. Most of the increase is due to diabetes and hypertension.

The increase in hypertension and diabetes translates into increased rates of stroke, heart failure, and myocardial infarction. Indeed, there has also been a remarkable increase in cardiovascular disease throughout the world. Coronary artery disease was once considered rare and was observed primarily in Europe and in the United States (22). By 1929, Platt (23) noted that coronary disease had increased in frequency such that it was commonly observed by the family practitioner; by 1940, cardiology was initiated as a discipline in the United States. By 1950, there were only 500 cardiologists in the United States, and, by 1960, the World Health Organization pronounced a world epidemic of cardiovascular disease. Today, there are >25 000 cardiologists in the United States performing >1 million coronary angiograms yearly, and >720 000 cardiovascular surgeries are performed annually (4). Cardiovascular disease is currently the major cause of death in the United States, accounting for 37% of all deaths, and is considered a contributing factor in an additional 21% of the population (4). Similar increases in coronary artery disease and cardiovascular mortality have also been observed in other countries (20).

Some have argued that there is no cardiovascular epidemic, because the absolute number of cardiovascular deaths in the United States and the calculated rates per population are currently decreasing (4). It has also been stated that the increase in hypertension simply reflects the increase in the aging population, because the average life span has increased from 47 y in 1900 to 77 y today (24). Furthermore, the increasing longevity of the population has been used as an argument that the increase in obesity may not be a disadvantage. However, these arguments are lacking. First, the observed decline in cardiovascular mortality rates is probably not due to a decrease in cardiovascular disease, but rather to the fact that we have developed better ways to control cardiovascular disease after it has developed. Today, we have antihypertensive agents, statins, antiplatelet drugs, and a host of surgical and nonsurgical treatments for those with coronary artery disease. Whereas it is true that an aging population will likely mean higher rates of hypertension, we are now observing hypertension in adolescents that cannot be explained by an aging population (13). Furthermore, in the 1939 study (10), only 12–13% of 50- to 55-y-old men had hypertension (and only 1.6% had systolic blood pressures >140 mm Hg); today, age-matched men have a hypertension frequency of 31%. Finally, the comment that obesity is an advantage because people are living longer negates the fact that, in the general population, longevity is greater in persons with a normal BMI than in those with a high BMI (25). It is more likely that increased longevity relates to better hygiene, a reduction in malnutrition, the introduction of antibiotics, and the increasing affluence of the world population.

THE PARALLEL EPIDEMIC OF SUGAR CONSUMPTION

Whereas today the intake of foods containing table sugar (sucrose) occurs with almost every meal, the introduction of sugar into the diet is relatively recent. Before the introduction of sugar, the primary sweetener had been honey, but because it was relatively rare and not mass produced, the majority of people (especially the poorer classes) had no sweeteners at all in their normal diet (26).

Sugar derived from sugar cane was first developed in New Guinea and in the Indian subcontinent and was a rare and expensive commodity that was introduced into Europe via Venice, Italy, and other trading ports during the Middle Ages. During this time, only royalty or the very wealthy could afford this luxury. However, by the late 1400s, Spain and Portugal began growing sugar cane in the Canary Islands, in Madeira, and in Silo Tome; this led to such wealth that King Emmanuel I of Portugal, "the
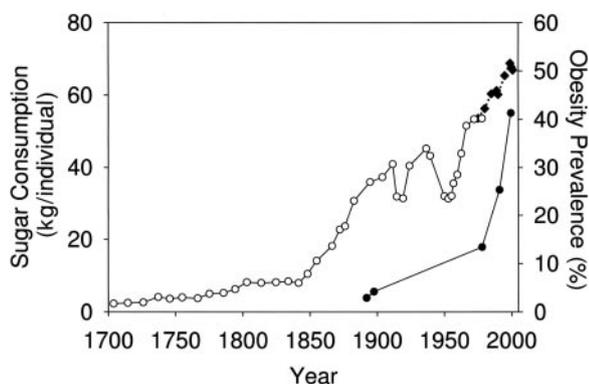
FIGURE 1. Sugar intake per capita in the United Kingdom from 1700 to 1978 (30, 31; ○) and in the United States from 1975 to 2000 (32; ◆) is compared with obesity rates in the United States in non-Hispanic white men aged 60–69 y (17; ●). Values for 1880-1910 are based on studies conducted in male Civil War veterans aged 50–59 y (18).

Fortunate" (1469–1521), sent life-sized sugar effigies of the Cardinals and the Pope to the Vatican in 1513 as a gift (27).

The discovery of the New World provided a mechanism for expanding sugar production. Christopher Columbus brought sugar cane to Santo Domingo on the island of Hispaniola (which is now Haiti and the Dominican Republic) on his second voyage in 1493; shortly thereafter, sugar plantations were established in the Caribbean islands, in the Guiana coasts, in Brazil, and eventually in the southern United States. Although initially an attempt was made to use Native Americans to work the plantations, a Catholic priest, Bartholomew de las Casas, requested King Ferdinand of Spain for the protection of the local Taino Indians because of the large numbers who had been killed or who were dying from smallpox or other diseases. So, in 1505, the first ship of African slaves departed for America to work the plantations. The next three and a half centuries witnessed the infamous "Triangle Trade," in which ships would sail to Africa, loaded with manufactured goods such as brass, copper, lead, salt, and gunpowder, which would be used to purchase slaves who were then shipped across the famed "Middle Passage" to the sugar plantations in the Caribbean and southern states. It is estimated that between 10 and 20 million Africans were brought to America during this period.

Whereas initially Portugal and Spain were the major importers of sugar, the capture of the Spanish settlement of Kingston, Jamaica, by the English in 1655 resulted in much of the sugar being exported to England. Sugar was such a desirable commodity that England began to hoard the sugar for its own people. Whereas in 1660, England exported 67% of its sugar to the rest of Europe, by 1753, this dropped to 5.5% (28). The increase in sugar production resulted in its increased availability to the public. Before the introduction of sugar, the primary diet was carbohydrate based, but it was primarily starch, consisting of a diet rich in barley, wheat, oats, and rye. Sugar had been used primarily as a costly medicinal. However, with the increased availability of sugar, it could also be used to sweeten chocolates, teas, and cakes. The average per capita sugar intake in England was 4 lb (1.8 kg) in 1700 and 18 lb (8.1 kg) in 1800, and it increased even more after the prime minister, William Gladstone, removed the sugar tax in 1874, which led to a mean consumption of 100 lb (45 kg) in 1950 (29; **Figure 1**).

The blockade of sugar importation to Europe by the British navy after 1700 caused a shortage of sugar to these countries. As

a consequence, techniques were developed to extract sugar from beets, and by the beginning of the 18th century, a thriving sugar beet industry was developing in Germany, France, and Austria. The combined production of sugar from sugar cane and beets led to a marked increase in world sugar production, from 250 000 tons in 1800 to 8 million tons in 1900 (33).

Sugar consumption continued to increase in the 1900s, with an overall doubling in the United States and the United Kingdom between 1900 and 1967 (34). By 1993, >110 million tons of sugar were produced worldwide (33). Whereas sugar intake continues to be marked in the industrialized nations, it is in the developing countries that the greatest increase in the rates of sugar consumption has been observed (35). By the early 1970s, an additional sweetener, high-fructose corn syrup (HFCS), was introduced in the United States, which had certain advantages over table sugar with relation to shelf life and cost. This sweetener, the composition of which is similar to that of sucrose, is used extensively to sweeten soft drinks, fruit punches, pastries, and processed foods. The combination of table sugar and HFCS has resulted in an additional 30% increase in overall sweetener intake over the past 40 y, mostly in soft drinks. Currently, consumption of these sweeteners is almost 150 lb (67.6 kg) per person per year (36), which has resulted in the ingestion of >500 kcal/d (37; Figure 1).

ARE THESE EPIDEMICS RELATED?

Keys (38) is credited with the discovery of an association of Western diets with the development of coronary artery disease. Keys focused on the relative increase in fat intake with a decrease in total carbohydrate intake, and this general finding ("nutrition transition") has been confirmed in numerous studies, which has led to the widespread recognition of the importance of fat intake in the development of heart disease. However, Yudkin (39) showed in the early 1960s that the Western diets high in fat are also high in sugar, and he proposed that sugar intake may also play an underlying role in the cardiovascular epidemic. In addition, recent history in the United States has shown that, although a low-fat intake has been promoted, rates of obesity have continued to increase as sugar consumption has continued. In addition, recent studies showing that a low-carbohydrate, high-fat diet has no adverse cardiovascular effects (40, 41) suggest that it is time to revisit the causes of the cardiorenal disease epidemic. In 2002, Havel's group (37) made the case that the fructose content of sugar may be the critical component associated with the risks of obesity and heart disease. Sucrose is a disaccharide consisting of 50% fructose and 50% glucose, and HFCS is also a mixture of free fructose and glucose of approximately the same proportion (55:45).

There are some striking epidemiologic associations between sugar intake and the epidemic of cardiorenal disease. For example, obesity was initially seen primarily in the wealthy, who would have been the only ones able to afford sugar. Also, the first documentation of hypertension, diabetes, and obesity occurred in the very countries (England, France, and Germany) where sugar first became available to the public. The rise in sugar intake in the United Kingdom and the United States (Figure 1) also correlates with the rise in obesity rates observed in these countries. Furthermore, the later introduction of sugar to developing countries also correlates with the later rise in their rates of obesity and heart disease. A series of epidemiologic studies linked the

ingestion of soft drinks to obesity, hypertension, and diabetes (42, 43) and the consumption of fruit juice and fruit punch to obesity in children (44, 45). Although these epidemiologic associations suggest a potential causal role, are there any direct experimental data to show that sucrose or fructose can induce obesity or hypertension?

SUGAR (FRUCTOSE) STUDIES IN HUMANS AND EXPERIMENTAL ANIMAL MODELS

Clinical studies have confirmed that sucrose (and particularly fructose) can induce weight gain and features of the metabolic syndrome. For example, serum triacylglycerols increased in young men receiving a diet supplemented with 200 g sucrose/d, whereas concentrations did not increase when starch was the primary carbohydrate (46). Hyperinsulinemia developed in one-third of these subjects (30). In another study, the administration of sucrose supplements resulted in weight gain, a significant rise in serum triacylglycerols, and a rise in systolic blood pressure (47). An increase in blood pressure was also observed in healthy adults fed a diet of 33% sucrose for 6 wk but not when diets of 5% or 18% sucrose were fed (48). Others have also reported that diets enriched in either sucrose (49) or fructose (50) cause impaired glucose tolerance and insulin resistance. Notably, most of these diets provided fructose in the range of 400–800 kcal/d, which is within the upper range of what is currently being ingested in the United States.

Rodents also develop features of the metabolic syndrome after ingesting sucrose. As in humans, it was shown that the active ingredient is fructose rather than glucose: feeding fructose to rats resulted in the metabolic syndrome, whereas equivalent amounts of glucose or starch did not induce these features (51). In addition to the metabolic syndrome, the administration of fructose resulted in the development of renal hypertrophy, afferent arteriolar thickening, glomerular hypertension, and cortical vasoconstriction (52). Furthermore, feeding fructose to rats with chronic renal disease (rats that have had five-sixths of their renal mass removed) resulted in an increased progression of the disease, as evidenced by worsening proteinuria, renal function, and glomerulosclerosis (53). Worsening of renal function was not observed in rat pairs fed dextrose (53).

It has been argued that the fructose studies in rodents should not be compared with human studies because the doses of fructose administered to rodents are not physiologic, inasmuch as they usually account for 60-70% of the diet. However, we recently found that lower doses of fructose (10% given in the water, resulting in one-half of the caloric intake, compared with the classic 60% fructose diet) can also induce hypertension and renal microvascular changes, although they are less severe (52).

MECHANISMS FOR FRUCTOSE-INDUCED METABOLIC SYNDROME

Fructose may cause obesity via several different mechanisms. First, Havel's group (54) conducted a clinical study that found that fructose may not cause the level of satiety equivalent to that of a glucose-based meal. Specifically, the differences in the effect of fructose and glucose consumption (consumed as beverages with 3 meals) on ad libitum food intake and hunger rating were observed on the day after the exposure to the sweetened beverages. The mechanism was related to the inability of fructose

to acutely stimulate insulin and leptin and to inhibit ghrelin, all factors that are known to affect the satiety center in the central nervous system. Yudkin (34) also argued that the sweetness of fructose (or sucrose) often makes food more palatable, and, indeed, the food industry has capitalized on this by frequently adding HFCS or sugar to normally nonsweetened foods (such as crackers) to enhance the taste. This may stimulate more food intake. Furthermore, mice fed fructose-sweetened water gain more weight than do mice given the same calories as starch, which suggests that fructose may also slow the basal metabolic rate (55).

One unique aspect of fructose is that it is the only sugar that raises uric acid concentrations, and this can be shown in both humans (56) and rodents (57). Fructose enters hepatocytes and other cells (including tubular cells, adipocytes, and intestinal epithelial cells), where it is completely metabolized by fructokinase with the consumption of ATP; unlike in glucose metabolism, there is no negative regulatory mechanism to prevent the depletion of ATP. As a consequence, lactic acid and uric acid are generated in the process, and uric acid concentrations may rise by 1–4 mg/dL after the ingestion of a large fructose-based meal (58).

Although the rise in uric acid concentrations has historically been viewed as simply a potential risk factor for inducing gout, recent studies suggest that this may be a key mechanism to explain how fructose causes cardiovascular disease. In addition, it also provides a mechanism to explain why rodents are relatively resistant to the effects of fructose (*see* below).

FRUCTOSE-INDUCED HYPERURICEMIA AS A MECHANISM FOR CARDIORENAL DISEASE

Nakagawa et al (51) recently showed in experimental animals that lowering uric acid concentrations could largely prevent features of the metabolic syndrome induced by fructose, including weight gain, hypertriacylglycerolemia, hyperinsulinemia and insulin resistance, and hypertension. The protective effect of lowering uric acid concentrations on the development of the metabolic syndrome was shown regardless of whether the uric acid concentrations were lowered by using a xanthine oxidase inhibitor or a uricosuric agent (51).

These studies were surprising, because most authorities had considered uric acid to be either biologically inert or an important antioxidant in the plasma (59). However, uric acid was found to have numerous deleterious biologic functions. For example, uric acid stimulates both vascular smooth muscle cell proliferation and the release of chemotactic and inflammatory substances (60–62), induces monocyte chemotaxis (63), inhibits endothelial cell proliferation and migration (64, 65), and causes oxidative stress in adipocytes, which results in the impaired secretion of adiponectin (66).

In animals, the effect of elevated uric acid concentrations is even more pronounced. For example, mildly hyperuricemic rats develop hypertension because of the inhibition of nitric oxide synthase in the macula densa, the stimulation of intrarenal renin, and a reduction in endothelial nitric oxide bioavailability (67). Over time, hyperuricemic rats develop renal arteriosclerosis that then causes the animals to develop a salt-sensitive form of hypertension (62). Hyperuricemic rats also develop slowly progressive renal disease with renal vasoconstriction and glomerular hypertension (68).

An increase in uric acid in animals with preexistent renal disease accelerates the progression of the disease (69).

Whereas human diseases such as obesity, renal disease, and cardiovascular diseases likely have complex and multifactorial origins, recent studies have suggested that uric acid is an independent risk factor for these diseases. Uric acid has now been found to be an independent predictor of hypertension in 15 of 16 published studies, including a recent report by the Framingham Heart Study group (70–85). Uric acid is also an independent predictor of obesity (86), hyperinsulinemia (87), and renal disease (88). Furthermore, uric acid concentrations are elevated in the vast majority (89%) of adolescents with new-onset hypertension, and in pilot studies, the lowering of uric acid concentrations was found to reduce blood pressure in these subjects (89, 90). A recent prospective, controlled trial also reported that the lowering of uric acid concentrations in patients with hyperuricemia and renal disease resulted in significantly slower renal progression and a significant (13 mm Hg) fall in systolic blood pressure that was not observed in the controls (91). Whereas more clinical studies are clearly needed, these data suggest that uric acid may contribute to the cardiorenal disease epidemic.

The mechanism by which uric acid causes these effects may involve a reduction in the concentrations of endothelial nitric oxide. Uric acid potently reduces the concentrations of endothelial nitric oxide in vitro and in vivo in experimental animals (64, 65). Hyperuricemia in humans is also strongly associated with endothelial dysfunction (92, 93), and lowering uric acid concentrations has consistently been shown to improve endothelial function after several weeks (94–98). In turn, a reduction in endothelial nitric oxide predisposes animals to develop features of the metabolic syndrome. For example, genetically modified mice that lack endothelial nitric oxide synthase develop many features of metabolic syndrome, including hypertension, hypertriacylglycerolemia, and insulin resistance (99).

Several potential mechanisms may explain how an impaired production of endothelial nitric oxide results in features of the metabolic syndrome. For example, a reduction in nitric oxide results in systemic and intrarenal vasoconstriction, renal microvascular disease, and systemic hypertension (100). Endothelial nitric oxide is also critical in mediating the increase in blood flow to the skeletal muscle in response to insulin, and blocking nitric oxide can result in higher blood insulin concentrations and peripheral insulin resistance (101). In turn, insulin stimulates the secretion of hepatic triacylglycerol (102).

It should be noted that obesity itself can also induce insulin resistance, in part by the intracellular accumulation of triacylglycerols (102). Once renal arteriosclerosis develops, hypertension also becomes salt sensitive and renal dependent (103). Finally, the progressive loss of renal function and mass will result in intrarenal hemodynamic changes that favor a continued decline in renal function (104). Hence, fructose- and uric acid–associated mechanisms are likely to be of more importance in the initial development of the metabolic syndrome phenotype and may become less important once obesity, hypertension, and renal disease become established.

WHY ARE AFRICAN AMERICANS SUSCEPTIBLE TO CARDIOVASCULAR DISEASE?

It is well known that African Americans have higher rates of obesity, hypertension, diabetes, kidney disease, and heart disease

(105). This increased rate of cardiorenal disease contrasts with a near absence of hypertension and obesity in studies performed in the early 20th century in blacks living in Africa (106, 107). It is interesting to speculate that African Americans may also have been exposed quite early to sugar. Early workers cut and bundled the sugar cane in the fields, pressed the cane in the local mills to get the sugary extract, and boiled this extract in the sugar houses to generate the sugar crystals and leftover molasses. Molasses (which is sucrose) was a staple in the early African American diet, and one wonders whether it may have played a role in the increased frequency of hypertension that was noted in early epidemiologic studies performed in the Caribbean and in Louisiana (108, 109). Recent studies also have documented that the sugar intake of African Americans is greater than that of whites (110, 111). Similar high sugar intakes were noted in studies of Australian Aborigines and Samoans living in New Zealand (112, 113). Furthermore, it is known that African Americans have higher concentrations of uric acid (114); in the African American Study of Hypertension and Kidney Disease, the average uric acid concentration was 8.3 mg/dL (115).

Other explanations are also possible, including the preferential survival during the early years of slavery of subjects with higher blood pressures, salt sensitivity, obesity and insulin resistance, and better wound healing (116). Indeed, African Americans with hypertension and renal disease have been found to have a higher frequency of a polymorphism for transforming growth factor-β (TGF-β) and elevated serum TGF-β concentrations (117). TGF-β is a cytokine important in wound healing and was recently shown to have a role in blood pressure (118). An increase in TGF-β could also explain the rapid progression of microvascular injury and renal disease characteristic of African Americans (119) and, by inducing microvascular disease, could also have a role in the induction of salt sensitivity (103).

A congenital mechanism has also been proposed. African Americans have a higher frequency of low-birth-weight infants, which has been linked to a low nephron number (120). In turn, a low nephron number is associated with the later development of hypertension, diabetes, and obesity (121). Interestingly, low-birth-weight infants are known to develop early hyperuricemia and endothelial dysfunction (122). Indeed, evidence that uric acid may have a role in this condition is mounting (123).

Finally, an environmental mechanism also seems likely. African Americans may be under more societal stress owing to lower socioeconomic conditions (124). They also have diets higher in sodium and lower in potassium (125).

CAVEATS

A key difficulty in proving that sugars play a participatory role in the epidemic of cardiorenal disease is separating the effect of fat intake and the effect of sugar intake. That is, survival for thousands of years was based on our ability to store triacylglycerol for survival during times when food was scarce. Since the industrial revolution, food has been plentiful, and obesity has increased because of the innate nature to store triacylglycerols in the face of excessive caloric intake. However, whereas an increased intake of calories as fat can cause obesity and obesity can lead to insulin resistance, it is our hypothesis that only sugars can directly lead to insulin resistance. In addition, for the past 20 y, there has been a push to lower fat intake, and the result of these

programs has been a marked increase in the prevalence of obesity. Interestingly, during this period, the level of fructose intake increased considerably.

Another difficulty in showing causation in human studies of the effect of fructose on the incidence of cardiorenal disease, independent of obesity, is that obesity and fructose intake track together. Thus, whereas animal studies have shown a causal effect of fructose on cardiorenal markers, independent of obesity, causation cannot be shown in human studies.

CONCLUSION

In conclusion, we propose that sugar intake, and particularly that of fructose, may have an important participatory role in the current cardiorenal disease epidemic and may also explain why certain subgroups, such as African Americans, are particularly prone to disease. This pathway may well be mediated, in part, by the unique ability of fructose to raise uric acid. This may also explain why rodents are relatively resistant to fructose, because these animals have lower uric acid concentrations owing to the presence of an enzyme (uricase) that degrades uric acid to allantoin. Indeed, when uricase is inhibited in the rat, fructose will cause a 5-fold greater increase in uric acid concentrations (57).

The observation that uric acid may play a key role in the process suggests that other mechanisms that raise uric acid concentrations may also play a role in the epidemic. In this regard, 17th and 18th century England is also famous for the enormous importation of fortified wines such as port and Madeira rich in sugar and lead (126). Lead can also cause hyperuricemia and hypertension. We have been able to block lead-induced hypertension by lowering uric acid concentrations (126). This would suggest that a low level of lead ingestion may act as an additional synergistic factor, particularly during the early part of the epidemic. Uric acid concentrations have increased within the general population in parallel with the epidemic of cardiorenal disease (8, 127).

If the hypothesis is correct that fructose has a role in the epidemic of cardiovascular disease, then a number of predictions should arise from future studies. First, fructose intake will be a risk factor for hypertension, insulin resistance, hypertriacylglycerolemia, obesity, type 2 diabetes, preeclampsia, chronic kidney disease, stroke, cardiovascular disease, and mortality. Second, reducing uric acid in patients with uric acid concentrations >6.0 mg/dL will improve endothelial dysfunction, decrease systemic vascular resistance, lower blood pressure, lower triacylglycerol concentrations, improve body weight, lower the risk of the progression of renal disease, and reduce cardiovascular disease risk. Third, low-fructose diets coupled with mild purine restriction will improve weight and reduce cardiovascular disease risk. Fourth, fructokinase will be identified as a key enzyme mediating the cardiorenal disease syndrome; genetic polymorphisms will be associated with cardiovascular disease risk, and blocking the enzyme will provide a novel way to prevent cardiorenal disease. Clearly, much more work needs to be done to prove or disprove this hypothesis.

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