Diabetes and Kidney Disease in American Indians: Potential Role of Sugar-Sweetened Beverages

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Abstract

Since the early 20th century, a marked increase in obesity, diabetes, and chronic kidney disease has occurred in the American Indian population, especially the Pima Indians of the Southwest. Here, we review the current epidemic and attempt to identify remediable causes. A search was performed using PubMed and the search terms American Indian and obesity, American Indian and diabetes, American Indian and chronic kidney disease, and American Indian and sugar or fructose, Native American, Alaska Native, First Nations, Aboriginal, Amerind, and Amerindian for American Indian for articles linking American Indians with diabetes, obesity, chronic kidney disease, and sugar; additional references were identified in these publications traced to 1900 and articles were reviewed if they were directly discussing these topics. Multiple factors are involved in the increased risk for diabetes and kidney disease in the American Indian population, including poverty, overnutrition, poor health care, high intake of sugar, and genetic mechanisms. Genetic factors may be especially important in the Pima, as historical records suggest that this group was predisposed to obesity before exposure to Western culture and diet. Exposure to sugar-sweetened beverages may also be involved in the increased risk for chronic kidney disease. In these small populations in severe health crisis, we recommend further studies to investigate the role of excess added sugar, especially sugar-sweetened beverages, as a potentially remediable risk factor.

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METHODOLOGY

A generalized search was performed using Entrez PubMed (September 2014), in which specific searches were performed for American Indian and obesity (1051 references), American Indian and diabetes (2058 references), American Indian and chronic kidney disease (174 references), and American Indian and sugar or fructose (4 references). We performed similar searches, substituting Native American, Alaska Native, First Nations, Aboriginal, Amerind, and Amerindian for American Indian. In addition, where appropriate, citations of baseline physiological data from Mexican Americans were used because they are often used as a proxy population to gain a deeper insight into epidemiology and genomics. All references were screened, and articles were selected on the basis of whether they provided general incidence and prevalence of obesity, diabetes, and CKD in the American Indian (primarily for the United States), as well as articles evaluating risk factors for these diseases.
ARTICLE HIGHLIGHTS

- Forty percent of the American Indian population is obese, and 18% have diabetes. Among American Indian tribes, Pima Indians have the highest incidence rates of diabetes in the world.
- Both genetic and nongenetic factors are involved in the increased risk for obesity, diabetes, and chronic kidney disease in the American Indian population.
- Recent studies suggest that intake of sugar-sweetened beverages may be an important and modifiable risk factor for obesity, diabetes, and chronic kidney disease.

for these conditions. An attempt was made to identify old sources that predate the earliest PubMed references. This was done by reviewing the oldest PubMed articles on the subject and reviewing and backtracking the references in those articles as well as by using Google Scholar to find those old articles. This approach allowed us to identify not only some reports on the Pima Indians from the 1800s but also a transcript of Father Font’s interaction with 1000 Pima Indians in 1775, which documented the presence of obesity in Pima women well before exposure to Western culture.

DIABETES, OBESITY, AND KIDNEY DISEASE IN THE AMERICAN INDIAN

Table 1 demonstrates the gravity of the present situation, with nearly 40% of adult American Indians being obese and 18% being diabetic. In parallel with an increased frequency of diabetes, an increase in CKD is noted. Most cases are due to diabetic nephropathy, although the incidence of other kidney diseases such as IgA nephropathy has also increased in some American Indian populations. American Indians who are diabetic also show a 7-fold higher risk for progression to end-stage renal disease (ESRD) as compared with whites with diabetes, and the incidence of ESRD is 60% higher in American Indians than that observed in whites. Interestingly, the incidence of ESRD in the American Indian has decreased in the United States over the past decade (Table 1). This may be due to a better managed chronic care model that accesses quality of care similar to that used for whites, which is based on better training and policy adaptation to the cultural and social mores of the Native American communities.

Despite higher incidence rates of obesity, the American Indian population was initially reported to have lower frequencies of hypertension and coronary artery disease. The Strong Heart Study, which is a cross-sectional study that enrolled American Indians from the Southwest, South Dakota, and Oklahoma, noted that by the 1990s the incidence rates of hypertension had become similar to those found in whites, with a higher prevalence of diabetes and obesity. In contrast, coronary artery disease and stroke remain lower in this population than in whites (Table 1). With the increasing incidence rates of hypertension, this pattern may change. Indeed, the frequency of peripheral vascular disease is currently similar in American Indians and whites. However, genetic studies show that Native American ancestry protects Hispanic Americans against peripheral vascular disease.

The overall pattern suggests a difference between American Indians and whites in that the incidence of obesity, diabetes, and CKD is higher in the American Indian population whereas that of stroke and coronary artery disease is lower. The lower incidence rates of vascular disease appear to be genetically based, but have decreased in recent years, likely because of the increasing frequencies of diabetes and obesity that confer increased risk for vascular complications. The genetic mechanisms underlying the reduced cardiovascular

<table>
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<tr>
<th>TABLE 1. Health Conditions of Native Americans and Whites</th>
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<tr>
<td>Health condition</td>
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<tr>
<td>Obesity (BMI &gt; 30 kg/m²) (age ≥ 18 y), 2004-2008 (%)</td>
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<tr>
<td>Diabetes (age ≥ 18 y), 2004-2008 (%)</td>
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<tr>
<td>Hypertension (age ≥ 18 y), 2004-2008 (%)</td>
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<td>ESRD, incidence, 2001 (cases per million)</td>
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<td>ESRD, incidence, 2011 (cases per million)</td>
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<tr>
<td>Chronic kidney disease (defined as eGFR &lt; 60 mL/min per 1.73 m²)</td>
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<tr>
<td>Coronary artery disease, 2006 (deaths per 100,000)</td>
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<td>Stroke, 2006 (deaths per 100,000)</td>
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*BMI = body mass index; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease.
*Data from the Family Core and the Sample Adult Core components of the 2004-2008 National Health Interview Surveys.
*Data from the United States Renal Data System, 2013.
*Data from the Kidney Early Evaluation Program (2000-2006).
*Data from the Third National Health and Nutrition Examination Survey, which show the prevalence of only chronic kidney disease stages III-V.
*Data from the Centers for Disease Control and Prevention Health Disparities & Inequalities Report.
risk are unknown, although the American Indian appears to have a higher frequency of the angiotensin-converting enzyme insertion (I) allelic variant, which may provide some protection from cardiovascular diseases, especially in people with diabetes.

Among the various American Indian tribes, the Pima Indians of the Southwest have a particularly high incidence of diabetes, with rates approaching 50%, along with high incidence of obesity and CKD. This suggests other genetic or environmental factors that may modulate this particular group.

CURRENT THINKING: ROLE OF ENVIRONMENTAL FACTORS IN INCREASING THE RISK FOR DIABETES AND KIDNEY DISEASE

The observations that obesity and diabetes were rare in most Native American tribes before exposure to Western culture suggest that environmental factors may drive the increased risk for obesity and diabetes in this population. An exception may be the Pima Indian (the Akimel O’odham) and the Yuma Indian of the Southwest, in whom obesity was reported in women as early as 1775, before exposure to Western culture. Nevertheless, the importance of environmental factors is evident by the 5-fold lower prevalence of diabetes and less frequent diabetic nephropathy in the Mexican Pima living in the State of Sonora than in the Pima living in the United States, which could be due to the Mexican Pima maintaining their native lifestyle based on subsistence farming. Similarly, a study in the 1970s reported low incidence rates of obesity and diabetes in the Tarahumara of the Sierra Madre mountains, a group that also maintained its native cultural and dietary lifestyle.

The reason why the introduction of Western culture increases the risk for obesity, diabetes, and CKD in the American Indian could be both dietary and nondietary factors. As a minority population, the American Indian has had more than its share of disparities, with some of the highest rates of poverty, poor education, and inadequate or absent health insurance in the United States (Table 2). All these factors are known to be associated with an increased risk for obesity, diabetes, and CKD. One likely mechanism may be via the relationship of these conditions with diet and exercise.

Native American Indian diets were typically crop based (maize, beans, and squash) in agricultural tribes or included lean meats and/or seafood in hunter-gatherer groups. More recent studies have found that pre-Columbian diets may have included less meat and more developed crops and wild root vegetables (such as wild rice). With Westernization, there was a gradual reduction in native foods in favor of diets that were typically high in fat, high in sugar, low in whole grains, lacking fruits, and low in fiber. The combination of these diets may be a significant risk factor for the development of obesity and metabolic syndrome. In addition, the introduction of technology (cars, television, and Internet) has resulted in an increase in sedentary lifestyle. For example, a study in Pima Indians found a relationship between the number of hours watching television and the risk for obesity.

Although obesity may have been present in the Pima Indian before exposure to Western culture, there is evidence that obesity and diabetes increased markedly after exposure to Western diet and culture. For example, obesity was already increasing in the late 1800s despite intermittent starvation due to the loss of crops, but under conditions in which Western foods (such as sugar) were available at trading posts. The first recorded case of diabetes was observed in 1902, which was remarkable as incidence rates in Europe at that time were in the range of 2 cases
Obesity was also observed in other tribes at that time, including the Papago and the southern Ute. By the 1930s, obesity and diabetes were more common in the Pima than in other Indian tribes and also in non-Hispanic whites (henceforth referred to as whites) living in New England. Nevertheless, by the 1960s high incidence rates of diabetes were observed in most American Indian tribes.14,23,40-43 By 1991, half of the Pima adults were diabetic, giving them the distinction of having the highest incidence rates of diabetes in the world. 

Social, cultural, and economic factors also affect the selection of healthy diets and physical activity. For example, physical activity in American Indian women has been reported to be increased in the better educated, those who are not married, and those whose personal network includes individuals who are physically active.

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<th>Table 3. Genetic Allelic Variants Associated With Diabetes, Obesity, and CKD in American Indians</th>
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<tr>
<td><strong>Gene</strong></td>
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<td>WFS1</td>
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<td>ENPP1</td>
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<tr>
<td>SLCT1A1</td>
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<tr>
<td>SLCT2A5</td>
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<td>ABCG2</td>
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<tr>
<td>PRKAG2 and others</td>
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<td>ABCA1</td>
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<tr>
<td>FTO</td>
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<tr>
<td>nAChR family</td>
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<td>CPTI</td>
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<td>TMRR5</td>
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<td>ABC11</td>
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<td>nAChRs</td>
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<tr>
<td>TMEM154</td>
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<tr>
<td>POU6F1-TCF19</td>
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<tr>
<td>LPP</td>
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<td>HNF1</td>
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*CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; eSRD = end-stage renal disease; HDL = high-density lipoprotein; OR = odds ratio; SNP = single nucleotide polymorphism.

*Mexican Americans.

*Combined effect of PRKAG2, SLCT1A1, UBE2Q2, PPSK1B, BCS1, and WDR72.

*Native Americans from Human Genome Diversity Project.*

*Alters the melanocortin receptor 4 pathway in the hypothalamus, which is involved in leptin signaling.
active. Conversely, low family income and lack of education are associated with the intake of poor-quality foods, including fast foods and foods rich in sugar. Indeed, there is an increasing economic disparity in which healthy foods tend to cost more than unhealthy, nutrient-poor foods with high sugar and fat content.

CURRENT THINKING: ROLE OF GENETIC FACTORS IN INCREASING THE RISK FOR DIABETES AND KIDNEY DISEASE

It is likely that genetics may be interacting with environmental factors, which results in an increased risk for obesity, diabetes, and CKD. In this regard, most studies suggest that the American Indian population resulted from several migrations that occurred 15,000 to 20,000 years ago. A small population living in the steppes of Beringia and who likely had origins from north central or northeast Siberia followed the coast of Alaska and Canada into the Americas as the glaciers receded (the Late Glacial Maximum). Three major linguistic groups—Amerindian, Na-Dene, and Aleut—Eskimo—are recognized, and on the basis of genetics, 5 mitochondrial clades—a, B, C, D, and X—and 2 Y chromosomal haplotypes—Q and C—were identified.

Today, the American Indian population is heterogeneous, with nearly 45% (2.3 million) being a mixture of ethnicities. For example, East Coast tribes have a high percentage of a tri-racial admixture of white, African, and Native, whereas many Plains and Western tribes have a relatively small percentage of admixture. Californian, Alaskan, and Pacific Northwest tribes have the additional contribution of Asian and Polynesian admixture. In addition, differences among American Indian tribes may exist because of factors such as relative attrition rates from illnesses (such as smallpox) that decreased the populations. All these factors provide challenges to the aggregate interpretation of genetic studies in the American Indian population.

Nevertheless, a number of gene polymorphisms have been linked with obesity, diabetes, and CKD in the American Indian population (Table 3). Given the historical studies that suggest that the Pima Indian may have a relatively greater predisposition to obesity and diabetes despite diets high in vegetables and fiber, we have separated the gene polymorphisms identified in the Pima from those observed in other American Indian tribes. Interestingly, several gene polymorphisms associated with leptin receptors and leptin signaling have emerged as risk factors for obesity in the Pima Indian. Leptin is an adipokine that has a key role in controlling appetite and energy balance, and altered function of leptin or leptin receptors can result in a marked increase in obesity. Nevertheless, these polymorphisms account for only a small percentage of obesity in the Pima.

ROLE OF SUGAR-SWEETENED BEVERAGES IN INCREASING THE RISK FOR OBESITY AND DIABETES IN THE AMERICAN INDIAN

The role of sugar-sweetened beverages in the pathogenesis of obesity and metabolic syndrome has recently received much attention. These beverages contain either table sugar (sucrose), which is a disaccharide containing fructose and glucose, or high fructose corn syrup, which is a sweetener containing a combination of fructose and glucose monosaccharides. Although early studies suggested that sugar-sweetened beverages might simply be a source of unnecessary and nutritionally poor (“empty”) calories, more recent studies suggest that the fructose component may actually have a direct role in causing obesity and metabolic syndrome. Specifically, studies in animals have shown that when fructose is metabolized there is a transient depletion of adenosine triphosphate in the cell, which results in nucleotide turnover and uric acid generation. This “side-chain” reaction has been shown to induce mitochondrial oxidative stress and inflammation that results in a reduction in energy production with a shunting of calories to fat along with the development of insulin resistance. Studies in humans have also shown that intake of sugar-sweetened beverages or fructose causes intrahepatic adenosine triphosphate depletion, uric acid generation, hepatic lipogenesis, hepatic insulin resistance, preferential visceral fat accumulation, and a reduction in energy expenditure.
it is not surprising that intake of sugar-sweetened beverages is closely associated with the development of obesity and diabetes in the general population.\textsuperscript{103-107} Indeed, most medical societies recommend reducing the intake of sugar-sweetened beverages because of concerns that they are playing a role in the obesity and diabetes epidemics.\textsuperscript{108-110}

Consistent with these findings, numerous studies have reported a high intake of sugar-sweetened beverages in American Indians, especially in the young, those less educated, and those with lower incomes.\textsuperscript{23,48,111-113} In a study of indigenous Cree Native American communities in Canada, drinking of sugar-sweetened drinks was associated with both obesity and impaired fasting glucose.\textsuperscript{114} A high intake of sugar-sweetened beverages has been reported in numerous Indian tribes, especially those living in the southwestern United States.\textsuperscript{111-113,115-119} One study reported that 86% of Navajo girls and 93% of Navajo boys drink sugar-sweetened beverages every day.\textsuperscript{112} A study of Zuni adolescents found that 21% of energy intake in girls and 13% of energy intake in boys was from sugar-sweetened beverages.\textsuperscript{120} Consistent with these findings is the observation that dental caries, which reflect intake of sugar, are 5-fold higher in Native American Indians.

Sugar intake can also explain the paradox of why poverty and low education were not associated with obesity and diabetes in the early 1900s. Studies at that time found that sugar intake was greater in the wealthy and that it was the sugar that was linked to diabetes.\textsuperscript{125} Over the past several decades, intake of sugar-sweetened beverages has increased in parallel with increasing incidence rates of obesity in the United States and is highest among the poor, among minorities, and in those who are inactive.\textsuperscript{47,126}

**SUGAR AND URIC ACID AND THEIR POTENTIAL ROLE IN INCREASING THE RISK FOR KIDNEY DISEASE IN THE AMERICAN INDIAN**

Intake of added sugar may also have a role in increasing the risk for CKD. In laboratory animals, the ingestion of fructose can cause and accelerate kidney disease.\textsuperscript{47,127,128} Clinical studies have also linked the intake of sugar-sweetened beverages with kidney disease.\textsuperscript{129} One potential mechanism could be the ability of fructose to increase the uric acid level, as hyperuricemia is emerging as a risk factor for the development of CKD.\textsuperscript{129} Although uric acid was once considered simply an inert biological waste product, recent studies show that it has proinflammatory and pro-oxidative effects on the kidney, resulting in microvascular and glomerular injury.\textsuperscript{130-132} Consistent with these findings, clinical studies have found that hyperuricemia is a strong independent predictor of the development of CKD and pilot clinical trials also confirm the beneficial effect of lowering the uric acid level on renal function in CKD.\textsuperscript{129,133,134} Ongoing larger clinical trials are in process and are required before any specific recommendation can be made, but the evidence suggests that hyperuricemia may be an important risk factor for CKD.

There have been relatively few studies on uric acid metabolism in the American Indian. Early studies suggested that serum uric acid levels observed in American Indians were similar to or lower than those observed in non-Hispanic whites,\textsuperscript{135,136} but a more recent analysis of data from the Strong Heart Family Study reveals an increase in serum uric acid levels in American Indians, with \(12\%\) to \(21\%\) having hyperuricemia (defined as \(>7.0\) mg/dL in men and \(6.0\) mg/dL in women; to convert mg/dL values to mmol/L, multiply by \(0.0259\)) depending on the region.\textsuperscript{66} To date, no studies have evaluated whether hyperuricemia in the American Indian is a predictor of the development of CKD as it is in other populations.

**Genetic Considerations.** Support for the sugar pathway would be greater if gene polymorphisms in fructose or uric acid metabolism were found in American Indians, which might increase the risk for obesity, diabetes, or CKD. In this regard, allelic variants in 3 urate transporters—URAT1, ABCG2, and SLC2A9—have been linked with hyperuricemia in American Indians in the Strong Family Heart Study, and the allelic variant in SLC2A9 has also been shown to strongly predict the presence of CKD by a reduction in estimated glomerular filtration rate.\textsuperscript{69,84} The allelic variant in URAT1 has also been linked with metabolic syndrome and obesity in white populations.\textsuperscript{37}

We have also identified via Yale’s ALFRED and Broad Institute’s ExAC databases (http://alfred.med.yale.edu/, http://exac.broadinstitute.org/, respectively) the presence of gene
polymorphisms in fructose metabolism, which appear markedly different in the American Indian than in other major ethnic groups in the United States. Two allelic variants in fructokinase (ketohexokinase)—rs2304681 and rs1131375 single nucleotide allelic variants (SNPs)—are present in higher frequencies in the American Indian population than in other populations. The T allele of the rs1131375 SNP (75% frequency in American Indians vs 20%-40% in other populations) is associated with higher fasting insulin and lower HOMA-B (homeostasis model assessment of beta cell function) values in a European cohort (from the MAGIC study).138 In contrast, the A allele of the rs2304681 SNP (also present in 75% frequency in American Indians vs 30%-40% in other populations) may protect against hyperuricemia and liver fibrosis in a mostly white cohort.139 Although this finding may appear contrary to an association between metabolic syndrome and its adverse effects, one must be careful while drawing conclusions for the American Indian population. Although in many studies an association has been found in European Americans, the effect is not present in Mexican Americans. Because Mexican Americans have 30% to 50% of American Indian heritage, they sometimes serve as a proxy for American Indians; however, the effect of epistatic disruption from admixture has not been sufficiently assessed.140,141 In fact, some studies indicate that admixture makes disease associations quite unpredictable. The rs1131375 SNP is also in the 3’ untranslated region, which is increasingly seen as an important predictor of protein expression and stability, increasing the potential complexity of their outcomes. Lastly, both principal component analysis and SNP association data have revealed that Native Americans often have “private” alleles that are globally rare while demonstrating high local frequency and uniqueness.142 This is exhibited by 3 SNPs—rs1063553, rs114353144, and rs371426923—that are labeled in Broad Institute’s ExAC browser as “Latino” but have no representation in any other population. SNPs of this kind are usually ancestral to the American Indian heritage of Hispanics and are 20% to 40% higher in frequency. The Pima often have allele frequencies different from those of the American Indian. With regard to epistasis, admixture, high-frequency private alleles, and a major dealth of exome elucidation in American Indians, these findings provide a compelling argument that further investigation of the relationship between fructose and metabolic syndrome phenotypes is warranted.

CONCLUSION

The American Indian, like many other ethnic groups, has seen a dramatic rise in obesity, diabetes, and CKD over the past century, which corresponds to the introduction of Western culture and diet. Although obesity and diabetes have become pandemic, the American Indian appears to have a lower frequency of cardiovascular disease than do whites, but this is changing with the increasing frequency of diabetes and obesity.

The Pima Indian may be distinct from most other American Indian tribes because there is evidence that obesity was present even before the introduction of Western cultures, although obesity and diabetes have since increased markedly. This suggests that genetic factors may be more important in this group, which is consistent with an increased frequency for gene polymorphisms involved in leptin-dependent pathways that have been observed in the Pima. Interestingly, the Maori and ancestral Polynesian groups may also have had some obesity and gout before the introduction of Western cultures.

This review documents that the American Indian is a population in severe health crisis. Identifying timely and remediable risk factors should be the primary goal for this relatively unique and underserved population. Although there are many genetic and nongenetic factors that likely cause an increase in risk for obesity and diabetes in this population, a case is made that the introduction of Western diet, and especially the consumption of added sugar such as sugar-sweetened beverages, is likely involved. Emphasis on improving health care should also be a public health priority. Clinical intervention studies investigating these potential remediable risk factors may help slow this epidemic. Most importantly, prevention and treatment strategies must include multicultural perspectives and interdisciplinary applications.

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Abbreviations and Acronyms: CKD = chronic kidney disease; ESRD = end-stage renal disease; SNP = single nucleotide polymorphism

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Potential Competing Interests: Drs Johnson, Lanasa, and Le are inventors listed on pending patent applications related to blocking fructose metabolism in metabolic and renal diseases (University of Colorado). Drs Johnson, Lanasa, Le, and Sánchez-Lozada are also founders of Colorado Research Partners LLC, which develops inhibitors of fructose metabolism. Dr Johnson is on the scientific board of Amway and XOERT Therapeutics.

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