Oxidative Stress as a Mechanism of Added Sugar-Induced Cardiovascular Disease

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Abstract

Keywords

- ▶ added sugars
- ▶ reactive oxygen species
- ▶ atherosclerosis
- ▶ hypertension
- ▶ coronary artery disease
- ▶ peripheral vascular disease

Added sugars comprising of table sugar, brown sugar, corn syrup, maple syrup, honey, molasses, and other sweeteners in the prepared processed foods and beverages have been implicated in the pathophysiology of cardiovascular diseases. This article deals with the reactive oxygen species (ROS) as a mechanism of sugar-induced cardiovascular diseases. There is an association between the consumption of high levels of serum glucose with cardiovascular diseases. Various sources of sugar-induced generation of ROS, including mitochondria, nicotinamide adenine dinucleotide phosphate-oxidase, advanced glycation end products, insulin, and uric acid have been discussed. The mechanism by which ROS induce the development of atherosclerosis, hypertension, peripheral vascular disease, coronary artery disease, cardiomyopathy, heart failure, and cardiac arrhythmias have been discussed in detail. In conclusion, the data suggest that added sugars induce atherosclerosis, hypertension, peripheral vascular disease, coronary artery disease, cardiomyopathy, heart failure, and cardiac arrhythmias and that these effects of added sugars are mediated through ROS.

Added sugars comprise of table sugar, brown sugar, corn syrup, maple syrup, honey, molasses and other sweeteners in the prepared and processed foods and beverages. Sugars (simple carbohydrates) refer to monosaccharides (glucose, galactose, and fructose) and disaccharides (sucrose [glucose + fructose] found in sugarcane, beets, honey, and corn syrup; lactose [glucose + lactose] found in milk products; and maltose [glucose + glucose] found in malt). Complex carbohydrates are glucose-containing polysaccharides, that is, starch. The American Heart Association recommends six teaspoons (24 g) of added sugar per day for women and nine teaspoons (36 g) per day for men or in other words added sugar should provide 100 cal/d for women and 150 cal/d for men, respectively.¹ The American Heart Association recommends that not more than 5% of calories should come from sugar.¹ High consumption of added sugars has a higher risk of cardiovascular disease and the associated risk factors.^{2,3} Benn et al,⁴ have reported that elevation of nonfasting glucose is associated with an increased risk of ischemic heart disease (IHD)

and myocardial infarction (MI). A high intake of sugar enhances the risk of coronary heart disease (CHD) in diabetic individuals using diuretics.⁵ The International Study of Macro/Micronutrients and Blood Pressure reported that daily consumption of every extra sugar-sweetened beverage increased the systolic arterial pressure by 1.6 mm Hg and the diastolic pressure by 0.8 mm Hg.⁶

The present review deals with the glucose and oxidative stress, cardiovascular disease, serum lipids, and inflammatory mediators, and the glucose-induced oxidative stress as a mechanism of cardiovascular diseases. A recent publication has shown that there is a significant correlation between the added sugar consumption and an increased risk of cardiovascular disease mortality.⁷

Reactive Oxygen Species

The formation of reactive oxygen species (ROS) is schematically depicted in **Fig. 1** and has been described in detail

Fig. 1 Figure shows the formation of various reactive oxygen species. GSH-P_x, glutathione peroxidase; SOD, superoxide dismutase.

elsewhere.⁸ The univalent reduction of oxygen (O_2), in the presence of a free electron generates superoxide anion ($O_2^{\cdot -}$). Hydrogen peroxide (H_2O_2) is formed by dismutation of $O_2^{\cdot -}$ by superoxide dismutase (SOD). H_2O_2 is not a free radical and is stable, lipid soluble, crosses membrane barrier, and has a longer half-life as compared with $O_2^{\cdot -}$. H_2O_2 is converted to H_2O and O_2 by catalase and glutathione peroxidase. H_2O_2 and $O_2^{\cdot -}$ in the presence of metal (iron or copper) via the Haber-Weiss or Fenton reaction generates hydroxyl radical ($\cdot OH$), which is very reactive and unlike H_2O_2 and $O_2^{\cdot -}$ which travel some distance from their site production, $\cdot OH$ acts locally at the site of generation. $O_2^{\cdot -}$ interacts with nitric oxide to produce peroxynitrite ($ONOO^-$), which at physiological pH generates peroxynitrous acid ($ONOOH$) and because of its very unstable nature it rapidly gives rise to $\cdot OH$.

Glucose and Generation of Reactive Oxygen Species

Glucose can generate ROS through various ways including mitochondria, nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase, sorbitol pathway, activated glycation, and insulin pathway.

Mitochondrial Generation of Reactive Oxygen Species

The increase in glucose metabolism generates reduced nicotinamide adenine dinucleotide and reduced flavin adenine dinucleotide, which increases the generation of $O_2^{\cdot -}$ that is converted to H_2O_2 and $\cdot OH$ in the mitochondria.⁹ The increased metabolic flux of glucose via mitochondrial glucose oxidation leads to an increased production of ROS.¹⁰ It has also been reported that fission-mediated fragmentation of mitochondrial tubules is associated with an enhanced production of mitochondrial ROS in hyperglycemic condition.¹¹ High glucose level upregulate thioredoxin-interacting protein, which is involved in high glucose-induced ROS production in the mitochondria.¹² The above data suggest that mitochondria is partly involved in the generation of ROS in hyperglycemia.

Glucose and Nicotinamide Adenine Dinucleotide Phosphate-Oxidase

The NADPH-oxidase system is a membrane-associated enzyme complex that lies dormant and is present in the vascular

endothelium and smooth muscle cells, cardiomyocytes, macrophages, and neutrophils. Activated NADPH-oxidase catalyzes the reduction of O_2 to $O_2^{\cdot -}$ by way of NADPH derived from the pentose phosphate pathway as shown in the equation below. $O_2^{\cdot -}$ is then converted to H_2O_2 and $\cdot OH$ as described above.

High-glucose concentration activates NADPH-oxidase.¹³ Baiteau et al¹⁴ have reported that the high glucose level activates cardiac NADPH-oxidase through a novel cardiac glucose transport system, the sodium-dependent glucose co-transporter, SGLT₁ (sodium-glucose linked transporter₁). NADPH-oxidase-induced generation of ROS in the heart depends upon NADPH generated by oxidative part of the pentose phosphate pathway.^{15,16} High glucose-induced NADPH-oxidase activation and subsequent ROS production has been implicated in apoptosis of umbilical endothelial cells.¹⁷ High glucose level activates NADPH-oxidase both in vascular smooth muscle cells and endothelial cells.¹⁸ NADPH-oxidase of macrophages is activated by hyperglycemia.¹⁹ High glucose level increases the activity of NADPH-oxidase in the endothelial microparticles.²⁰ The data suggest that added glucose can generate ROS through activation of NADPH-oxidase.

Glucose, Advanced Glycation End Products, and Reactive Oxygen Species

Advanced glycation end products (AGEs) are a heterogeneous group of molecules formed from nonenzymatic reaction of reducing sugars with amino group of proteins, lipids, and nucleic acids.²¹⁻²³ There are three pathways for the formation of AGEs from glucose: the Millard reaction, oxidation of glucose, and polyol pathway.

Millard Reaction

In Millard reaction glucose attaches to free amino acids of proteins nonenzymatically to form a Schiff base which spontaneously rearranges to form the Amadori product. These initial reactions are reversible. Subsequent reactions lead to the formation of AGEs through oxidation, degradation, and rearrangement. Oxidation of the glycated product is known as glycoxidation or the Millard reaction. Some of the AGE products include Ne-carboxymethyl-lysine, Ne-carboxyethyl-lysine, pyrraline, pentosidine, and argpyrimidine. There are other ways by which glucose can form AGEs.

Oxidation of Glucose

Auto-oxidation of glucose and the peroxidation of lipids into dicarbonyl derivatives lead to the formation of AGEs.²⁴ These dicarbonyl derivatives are glyoxal, methylglyoxal (MG), and 3-deoxyglucosone, and interact with monoacids to form AGEs. MG is the product of the glycolytic pathway formed through spontaneous transformation of triose phosphate.²⁵

MG along with 3-deoxyglucosone and glyoxal are the major sources of AGEs.²⁶ MG reacts oxidatively with arginine or lysine residue of proteins to form AGEs.²⁷

Polyol Pathway

The other pathway for the formation of AGEs from glucose is the polyol pathway. In this pathway glucose is converted to sorbitol by aldose reductase and then to fructose by sorbitol dehydrogenase. Fructose-3-phosphate, a metabolite of fructose is converted into α -oxaldehyde which interacts with monoacids to form AGEs.²⁸

AGEs interact with its cellular receptor RAGE (receptor for AGEs) and activates nuclear factor kappa-B (NF- κ B)²⁹ and generate ROS.^{30,31} NF- κ B increases the gene expression of cytokines (interleukin [IL]-1, IL-6, IL-8, tumor necrosis factor- α) and adhesion molecules (vascular cell adhesion molecules-1 [VCAM-1], intercellular adhesion molecule-1 [ICAM-1]).^{8,29,32} Cytokines are known to activate NADPH-oxidase, which generates ROS.³³⁻³⁵

Circulating AGEs are positively correlated with high sensitivity C-reactive protein (hs-CRP).³⁶ hs-CRP has been reported to increase the generation of ROS by neutrophils.³⁷ These data suggest that AGEs can increase the levels the ROS through activation of RAGE, activation of NF- κ B increases cytokines resulting in activation of NADPH-oxidase, and subsequent formation of ROS. hs-CRP generates ROS from neutrophils.

Insulin and Reactive Oxygen Species

Glucose intake increases the secretion of insulin.^{38,39} Insulin activates a plasma membrane enzyme system with the properties of NADPH-oxidase resulting in the generation of H₂O₂.⁴⁰⁻⁴² Goldstein et al⁴³ reported that insulin-induced generation of H₂O₂ is through activation of NOX₄, a homologous family of NADPH-oxidase. Espinosa et al⁴⁴ have also shown that insulin generates H₂O₂ through increased expression of NOX₄ a homologous family of NADPH-oxidase. The data suggest that insulin increases ROS through activation of NADPH-oxidase.

Uric Acid and Reactive Oxygen Species

Fructose in sugar raises uric acid in human⁴⁵ and rodents.⁴⁶ Uric acid scavenges carbon centered and peroxy radicals in hydrophilic environment, but cannot scavenge lipophilic radicals and cannot break the radical chain propagation within the lipid membrane.⁴⁷ The antioxidant activity of uric acid is in the plasma and body fluids only. Uric acid is a pro-oxidant and generates ROS in various ways⁴⁸ including interacting with peroxynitrite⁴⁹ and oxidized lipids.⁵⁰ The data suggest that fructose produces ROS through various mechanisms.

Sugar, Reactive Oxygen Species, and Cardiovascular Diseases

Atherosclerosis

In the segment described above, we have shown that added sugar is involved in the generation of ROS, and increased expression of cytokines and cell adhesion molecules. ROS have been implicated in the initiation and progression of hypercholesterolemia-induced atherosclerosis.⁵¹⁻⁵⁶ The oxidative hypothesis of the development of atherosclerosis is

detailed elsewhere.⁵⁶ In short, low-density lipoprotein cholesterol (LDL-C) is mildly oxidized to minimally modified LDL (MM-LDL), which stimulates smooth muscle cells and endothelial cells to produce monocyte chemoattractant protein-1 (MCP-1). ROS increases expression of cell adhesion molecules ICAM-1, VCAM-1, and endothelial leukocyte adhesion molecules on the endothelial cells.⁵⁷⁻⁵⁹ Monocytes adhere to the endothelial cell surface with the help of cell adhesion molecule. MM-LDL is further oxidized to oxidized LDL (OX-LDL). MCP-1 and OX-LDL helps in the migration of monocyte to the subendothelial area. Monocyte/macrophage gets differentiated by the help of monocyte colony stimulating factor released from endothelial cells by MM-LDL. The differentiated macrophage develops receptor for OX-LDL, which is picked by macrophages to form foam cells. Macrophage generates numerous growth factors leading to the formation of collagen, elastic fiber, and protein and transcription of smooth muscle cells. Smooth muscle cell proliferation, and migration, synthesis of connective tissue and matrix, migration of monocytes and formation of foam cells results in the development and progression of atherosclerosis.

Hypertension

About 25% people with type-1 diabetes and 80% with type-2 diabetes have high blood pressure. Diet rich in high fructose, a key ingredient in corn syrup, can produce high blood pressure. Studies in animals have shown an association between the sugar intake and development of hypertension.⁶⁰ Fructose leads to hypertension in dogs⁶¹ and rats.^{62,63} A diet containing excess sugar induces hypertension in F344 and F1-hybrid rat.⁶⁴ Fructose ingestion raises blood pressure in healthy young humans.⁶⁵ There is enough evidence to show that sugar (fructose) raises blood pressure. Here, we are going to discuss about the role of glucose-induced ROS in the development of hypertension in experimental animals and in humans.

An increased level of ROS precedes the development of hypertension in spontaneously hypertensive rats (SHRs).⁶⁶ There are increased levels of thiobarbituric acid reactive substances (TBARs) and F₂ α -isoprostane the markers of oxidative stress, tissue concentrations of H₂O₂ and O₂⁻ and activation of NADPH-oxidase and xanthine oxidase, decreased levels of nitric oxide and antioxidant enzymes in experimental hypertension.⁶⁷⁻⁶⁹ The generation of O₂⁻ is increased in vasculature of SHRs⁷⁰ and deoxycorticosterone acetate salt sensitive hypertension.⁷¹ There is attenuation and prevention of hypertension with antioxidants.^{72,73}

Hypertensive patients have higher serum levels of H₂O₂ compared with control subjects.⁷⁴ There is an increased production of ROS by polymorphonuclear leukocytes in hypertensive patients.^{75,76} Patients with hypertension (essential, salt-sensitive, and renovascular) have increased levels of TBARs, 8-isoprostane.⁷⁷⁻⁷⁹ Many experimental models of hypertension have indicated that there is an increased level of ROS and decreased levels of antioxidants or both.⁸⁰⁻⁸² It is clear that ROS levels are elevated in hypertension. Now the question is how ROS induces hypertension?

ROS can induce vascular contraction directly or indirectly via endothelin-1 or destruction of nitric oxide (a vasodilator).

Let us first consider the direct effect of ROS on vasculature. Bharadwaj and Prasad⁸³ reported that O_2^- produces a contraction of the isolated rabbit aorta that is endothelium-dependent. They also reported that H_2O_2 produced contraction in isolated rabbit aorta.⁸⁴ In vivo studies Prasad et al⁸⁵ reported that xanthine plus xanthine oxidase-induced ROS increased systemic and pulmonary vascular resistance in anaesthetized dogs. Polymorphonuclear leukocyte-derived ROS increases the total systemic and pulmonary vascular resistance.⁸⁶ The other possibility of ROS-induced hypertension is through production of endothelin-1, a vasoconstrictor. ROS increases the production of endothelin-1 in mesangial cells.⁸⁷ Vascular smooth muscle contraction is dependent upon intracellular calcium. ROS increases intracellular calcium through release from endoplasmic reticulum. O_2^- increases intracellular Ca^{2+} in cultured human myocardial cells.⁸⁸ Superoxide anion,^{89,90} H_2O_2 ,^{90,91} and $OH^{\cdot}$ ⁹² increase the intracellular Ca^{2+} in cultured vascular endothelial cells.

The other mechanism of ROS-induced hypertension could be the ROS-induced endothelial dysfunction. Nitric oxide (NO) is endothelial-derived relaxing factor.⁹³ ROS can damage endothelial cells and reduce the production of NO. O_2^- can deactivate NO by combining with it and producing other more active radicals such as peroxynitrite and $OH^{\cdot}$.^{94,95} ROS would reduce the bioavailability of NO and hence vasoconstriction.

ROS by damaging the endothelial would reduce the production of prostacyclin, which is a vasodilator. ROS also reduces the capacity of the cells to convert arachidonic acid to prostacyclin.⁹⁶ The reduction in the production of vasodilators in the endothelium will allow the circulating catecholamine to produce unopposed constriction of the blood vessels and hence raise the blood pressure. Sucrose consumption increases the sympathetic activity in the rat.⁹⁷ It has been reported that introduction of starch and sugars into human nutrition increases sympathetic activity.⁹⁸ Increase in the sympathetic activity would raise the blood pressure. These data suggest that ROS through various mechanisms could induce hypertension.

Coronary Artery Disease

There is an association between elevated fasting plasma glucose and increased risk of IHD and MI in people with or without diabetes.^{99,100} Benn et al⁴ using Mendelian randomization approach reported that both observational and genetic lifelong elevated nonfasting or fasting plasma glucose levels are associated with increased risk of IHD and MI. Intensive glycemic control in diabetic patients is associated with a 15% reduction in the risk of IHD.¹⁰¹ High blood sugar is a risk for the heart diseases. It is reported that glycated hemoglobin a measure of long-term blood glucose level, is an independent risk for CHD in both diabetic and nondiabetic subjects.¹⁰² Reports from the Nurses Health Study show that women with high glycemic blood had an increased risk for CHD (twofold risk during 10 years follow-up).¹⁰³ High sugar consumption is associated with an increased cardiovascular disease in both within the country and across countries.¹⁰⁴ There is an evidence that consumption of high amount of added sugar especially sugar-

sweetened beverages increases the risk of cardiovascular diseases.^{2,3} There is a significant association between added sugar consumption and increased risk for mortality from cardiovascular diseases.⁷ A high level of sugars also increases the risk factors for CHD. It is known that diets high in sucrose, glucose, and fructose increase the plasma levels of triglycerides.¹⁰⁵⁻¹⁰⁷ There is an inverse association between dietary sucrose and high density lipoprotein-cholesterol (HDL-C).¹⁰⁷ Consumption of beverages containing high sugar increases inflammation¹⁰⁸ and proinflammatory cytokines.¹⁰⁹

Buildup of atherosclerotic plaques in the coronary artery reduces blood flow to the myocardium resulting in symptoms ranging from angina to heart attack. Prolonged ischemia leads to cell necrosis. Ischemia can further increase the formation of ROS through xanthine-xanthine oxidase pathway which would further damage the myocardium.

The most important risk factors for CHD include hypercholesterolemia,^{110,111} diabetes,^{111,112} cigarette smoking,¹¹³ and hypertension.¹¹⁴ Hypercholesterolemia increases the generation of ROS through various ways.^{56,115} Hypercholesterolemia may increase the activity of oxidant-producing enzyme system: NADPH-oxidase, xanthine oxidase,¹¹⁶ and myeloperoxidase¹¹⁷ resulting in the formation of ROS. Oxidative stress in IHD could also be due to formation of $\bullet OH$ through interaction of O_2^- and NO.^{94,95} According to oxidative hypotheses of atherosclerosis,⁵¹⁻⁵⁶ oxidation of LDL assists in the formation of foam cells and contributes to various proatherogenic processes. Atherosclerosis and rupture of the atherosclerotic plaques of the coronary artery play a major role in the development of IHD. The facts that hypercholesterolemia produces atherosclerosis in animal models,⁵¹⁻⁵³ and antioxidants suppress hypercholesterolemic atherosclerosis^{51-53,118,119} suggest that ROS play a role in the development of atherosclerosis. This also suggests that ROS are involved in the development of IHD. If this is the case then IHD should be associated with an increase in levels of the ROS. As such it has been reported that serum levels of malondialdehyde, a parameter of increased levels of ROS are elevated in patients with CHD.¹²⁰⁻¹²²

Cardiomyopathy

There are very few articles suggesting the role of sugars in cardiomyopathy. It has been reported that consumption of high fructose diet (32% sucrose solution) for 10 weeks reduced the ejection fraction by 8% in the heart of rats.¹²³ Administration of 10% fructose solution for 2 weeks to Wistar rats produces left ventricular dysfunction measured by the left ventricular elastance a measure of left ventricular contractility independent of preloads, afterload, and heart rate.¹²⁴ Chang et al¹²⁴ also reported that these rats had increased end-diastolic volume. Davidoff et al¹²⁵ and Dutta et al¹²⁶ showed that consumption of high-sucrose diet (68% total energy) reduced the contractility of isolated cardiomyocytes in rats. In vivo studies using echocardiographic assessment of cardiac function in diabetic mice showed that there is systolic and diastolic dysfunction.¹²⁷ Van den Bergh et al¹²⁸ assessed the hemodynamic changes in type-2 diabetic db/db mouse and observed a reduction in the cardiac contractility. It

is also known that diabetic cardiomyopathy is associated with hyperglycemia.^{129–131} This is also supported by the fact that insulin reverses the diabetic cardiomyopathy in rats.¹³² Cardiomyopathy in diabetes may be due to increased levels of ROS. There are evidences that the levels of ROS are elevated in diabetes. Paolisso and Giugliano¹³³ reported that plasma free radical concentrations are positively correlated to fasting plasma insulin in patients with type-2 diabetes. Increased serum levels of malondialdehyde (MDA), an index of levels of ROS, have been observed in patients with type-2 diabetes.^{134,135} There is an increase in the O₂⁻ levels in serum of diabetic patients.¹³⁶ Increases in the serum levels of MDA have also been reported in type-1 and type-2 diabetic rats.^{137–139} It is evident that sucrose-induced cardiac dysfunction and diabetic cardiomyopathy is associated with hyperglycemia. It is also known that sugar increases the formation of ROS. Is there any evidence that ROS induce cardiac dysfunction and decreases myocardial contractility?

It has been reported that xanthine–xanthine oxidase-generated ROS⁸⁵ and polymorphonuclear leukocyte-derived ROS⁸⁶ reduce the myocardial contractility and cardiac function measured hemodynamically in dogs. Prasad et al¹⁴⁰ also reported that xanthine–xanthine oxidase-derived ROS reduced the cardiac function and contractility in anesthetized dog and reduced the left ventricular pressure in the isolated perfused rabbit heart. They also reported that SOD, an antioxidant enzyme prevented the xanthine–xanthine oxidase-induced reduction in left ventricular pressure in the isolated perfused rabbit heart. The above data suggest that sugar induces cardiomyopathy through the generation of ROS.

Heart Failure

Added sugars could produce heart failure because it would lead to IHD and cardiomyopathy. The details of sugar and IHD and cardiomyopathy have been described above.

Cardiac Arrhythmias

Although, there are numerous unauthenticated information regarding the role of sugars in the development of cardiac arrhythmias only a few articles are available dealing with this subject. Patients with diabetes have a 40% greater risk of developing atrial fibrillation. Epidemiological studies have reported an association between diabetes or elevated blood glucose and risk of atrial fibrillation.^{141–143} However, there are few studies which reported no association between diabetes or elevated glucose and risk of atrial fibrillation.¹⁴⁴ This discrepancy could be due to inclusion of obesity, which produces diabetes and atrial fibrillation. The other reason could be that the studies were not designed to focus on diabetes. Recently, in a population-based case–control study, Dublin et al¹⁴⁵ have observed that diabetes was associated with higher risk of atrial fibrillation and the risk was higher with longer duration of treated diabetes and worse glycemic control. They also reported that patients receiving treatment for diabetes had a 40% greater risk of atrial fibrillation as compared with nondiabetics. Beshai J. F. from Heart Rhythm Center at the University of Chicago has stated that fluctua-

tions in blood sugar levels and changes in insulin levels can lead to atrial fibrillation in diabetics.

Lactose causes cardiac arrhythmias in water flea *Daphnia pulex*.¹⁴⁶ Excess sugar intake causes cardiac arrhythmias because sugar causes fluctuation in insulin and adrenalin. Insulin¹⁴⁷ and adrenalin¹⁴⁸ induce cardiac arrhythmias.

Do ROS induce cardiac arrhythmias? There are some data from animal studies and in humans, which suggest that excess ROS are involved in the pathogenesis of cardiac arrhythmias. Morita et al¹⁴⁹ have reported that perfusion of H₂O₂ in fibrotic rat and rabbit heart in Langendorff preparation induces cardiac arrhythmias. ROS have been implicated in the cardiac arrhythmias.^{150–152} The data suggest that sugar-induced cardiac arrhythmias are mediated through ROS.

Peripheral Arterial Disease

Peripheral arterial disease (PAD) is a circulatory disorder that affects blood vessels outside the heart and brain. PAD is due to atherosclerosis characterized by atherosclerotic occlusive disease of the lower extremities and is a marker of atherothrombotic disease in other vascular beds such as coronary artery, carotid artery, and cerebral artery. Prevalence of PAD is 12 to 14% in the general population, but is 20% in the individuals above the age of 70.¹⁵³ Overall, 30% of diabetics suffer from PAD, and 20% of symptomatic patients have PAD.¹⁵⁴ Diabetes, smoking, hypercholesterolemia, C-reactive protein, which are the risk factors for atherosclerosis are also risk factors for PAD. High intake of sugar increases insulin level in some individuals, but not all, and that these individuals are susceptible to the effect of sucrose for occlusive arterial disease.¹⁵⁵

Hyperglycemia in diabetes would produce ROS through various mechanisms already described in the section “glucose and generation of reactive oxygen species” of this review. ROS have been implicated in the development of atherosclerosis, which has been described in the section “atherosclerosis” of this review.

These data suggest that sugars are involved in the development of PAD through the generation of ROS.

Comments

The American Heart Association recommends that not more than 5% of calories should come from sugar.¹ It has been recommended that women should not take more than 6 tsp/d and men should not take more than 9 tsp/d of added sugar. The weight varies among men and women. If a man weighing 50 kg and another man weighing 80 kg consume similar amounts of sugar, that is, 9 tsp/d of added sugar, the one with a lower weight would have more adverse effects as compared with the other with a higher weight. There should be a guideline where the normal consumption of sugar should be based on the weight range. Some of the top sources of added sugar diet are shown in ►Table 1. The population should be advised to reduce the consumption of a diet containing large amounts of sugars.

From the literature,¹⁵⁵ it appears that sugar consumption increases the levels of insulin in some individuals but not in

Table 1 Some of the sources of added sugars

Source	Amount of sugar (g)
12 ounce can of regular soda	36.0
16 ounce bottle of sugar-sweetened ice tea	46.0
20 ounce bottle of lemon-lime soda	64.0
Plain chocolate (100 g)	62.0
Chocolate spread (100 g)	57.10
Cola (100 g)	10.9
Sweetened fruit juice (100 g)	9.80
Fruit pastilles (100 g)	59.30
Iced cakes (100 g)	54.0
Chocolate-coated biscuits (100 g)	45.80
Frosted corn flakes (100 g)	37.0
Fruit yogurt (100 g)	16.60
Tomato ketchup (100 g)	27.5
Stir-in sweet and sour sauce (100 g)	20.20
A slice of apple pie	20.0
Half cup of ice cream	14.0

Source: 1. Top sources of added sugars in our diet—NHS choices.

Available at: <http://www.nhs.uk/livewell/goodfood/pages/top-sources-of-added-sugar-in-our-diet.aspx>. Accessed February 17, 2014.

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all and the individuals with increased levels of insulin are prone to develop occlusive arterial disease. In this review, we have discussed that both glucose and insulin increases the levels of ROS, which have been implicated in the development of cardiovascular disease. It is not clear, then why only those people who have high insulin levels with consumption of high sugars develop occlusive arterial disease. The most recent data^{38,39} suggest that glucose increases the secretion of insulin in all individuals. It appears that both glucose and insulin take part in the development of cardiovascular diseases via an increased generation of ROS.

Conclusions

The data suggest that added sugars are involved in the development of atherosclerosis, hypertension, peripheral vascular disease, coronary artery disease, cardiomyopathy, heart failure, and cardiac arrhythmias. The data also suggest that the cardiovascular diseases are mediated through ROS generated by sugars.

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Conflict of Interest

The authors have no conflict of interest to disclose.

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