Is there a link between soft drinks and erectile dysfunction?

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KEY WORDS

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ABSTRACT

This review focuses on the potential role of soft drinks, particularly the sugar component, in the pathogenesis of erectile dysfunction (ED). We analyzed the hypothetical link between metabolic disorders, induced by sweetened soft drinks overconsumption, and ED. High caloric intake, high refined-carbohydrates, and high fructose corn syrup (HFCS) content and less satiety are main factors responsible for metabolic disorders contributing to ED development. Regular diet mistakes among human males, such as soft drink consumption, may lead to slow and asymptomatic progression of ED, finally resulting in full claimed manifestation of ED.

INTRODUCTION

A soft drink is a non-alcoholic beverage, typically carbonated and sweetened. Soft drinks influence on human health is surrounded by myths and controversy. It is well known that soft drinks have detrimental metabolic effects nowadays and their consumption should be limited. However, men do not limit the volume of soft drinks in their diet and consume them much more often than woman [1]. The number of overweight adult males has tripled during the last three decades due to changing food and beverage diet patterns [2]. Soft drinks are the source of superfluous calories because of low satiety resulting from fluid consistency and high carbohydrate content [3]. Average soft drink consumption is estimated to be 100 liters per year. Regular consumption of soft drinks (one or more soft drink per day) is correlated with an excessive energy intake that induces weight gain (a 330 ml soft drink contains approximately 150 kcal) [4]. It was investigated that reducing intake by 100 kcal/day would eliminate 71.2 million cases of obesity in the USA [5].

This review focuses on the potential role of soft drinks, particularly the sugar component, in the pathogenesis of erectile dysfunction (ED). The hypothetical link between metabolic disorders, induced by sweetened soft drink overconsumption, and ED was analyzed. ED is the inability to develop and maintain an erection for satisfactory sexual intercourse [6]. Large studies found an association of ED with dyslipidemia, impaired glycemic control, central obesity, and hypertension [7]. These systemic risks factors cluster to clinically diagnosed metabolic syndrome (MetS). Corona et al. reported that 96.5% of obese men with MetS had ED [8]. MetS components were proven to be the result of soft drink overconsumption according to the NAHNES III study (National Health and Nutrition Examination Survey) [4]. High caloric intake, high refined-carbohydrates, and high fructose corn syrup (HFCS) content, and less satiety are the main factors responsible for the metabolic disorders related to soft drink overconsumption. One soft drink a day during a period of 20 years is enough to increase the risk of MetS to 48% [9].

Refined-carbohydrates

Penile erection is an effect of hemodynamic changes in the vascular bed. The most important factor triggering hemodynamic changes during erection is nitric oxide (NO). Endothelium derived NO is known to be the most potent endogenous vasodilator responsible for relaxing afferent blood vessels to the corpus cavernosum. NO is formed by nitric oxide synthase (NOS), which exists in three isoforms: neuronal (nNOS), endothelial (eNOS), and inducible (iNOS) [10]. Consumed soft drinks contain great amounts of refined carbohydrates such as sucrose. A refined-carbohydrate rich diet was shown to induce endothelium dysfunction, due to altered carbohydrate metabolism [11]. Soft drinks are characterized by a high glycemic index and can raise blood sugar levels quickly. This in turn triggers the release of insulin in an attempt to normalize the blood sugar. Hyperglycemia increases oxidant stress that arises due to several mechanisms such as hyperglycemic pseudo-hypoxia, accumulation of sorbitol in endothelial cells, and glucose autoxidation [12, 13]. Reactive oxygen species (ROS) are produced in mitochondria by the cellular disturbances in glucose and lipid metabolism. Oxidative stress occurs when there is an imbalance between the pro-oxidants and the ability of the antioxidants to scavenge excess production of ROS. ROS rapidly scavenge NO within the vascular wall decreasing its biological half-life [14]. Hyperglycemia is physiologically reduced by insulin released from the pancreas. This hormone also stimulates hepatocytes to release VLDL (very low destiny lipoprotein) and LDL (low destiny lipoprotein), which are major triglyceride carriers [15]. Increased triglycerides and LDL levels contribute to the vascular damage and trigger an inflammatory response, resulting in monocyte's adhesion to the endothelial cells [16]. This process is responsible for arteriosclerosis progression. ED is considered to be an early arteriosclerosis manifestation [17].

Prolonged duration of hyperglycemia causes insulin resistance, which is an important pathophysiological basis of endothelium dysfunction [18]. Insulin has important hemodynamic actions that involve stimulation of the production of nitric oxide (NO) from endothelium and endothelial cells cell cycle regulation [19]. These actions are impaired after the development of insulin resistance and lead to the establishment of a reverberating negative feedback between insulin resistance and endothelium dysfunction [20].

Endothelial dysfunction refers to impairment of many significant functions of the endothelium including anti-inflammatory and antiproliferative characteristics as well as vasodilatation. In such conditions, the release of vasodilating factors is decreased in the penile vascular bed including cavernous bodies as well [21]. The small diameter (1-2 mm) and the high content of smooth endothelial and muscular cells by unit of tissue volume determine a higher cavernous arteries susceptibility to damage induced by hyperglycemia, oxidative stress, and other endothelium damaging factors [22]. Given the role of a rich refined-carbohydrate diet in impairing

endothelium function through glucose and lipid metabolism disturbance, it is likely that erectile dysfunction is associated with high soft drink consumption.

ED was correlated with less sensitivity of the cavernosal artery for vasoactive medications, such as nitrates, calcium antagonists, angiotensin-converting enzyme inhibitors, and β-blockers [23]. The major causes of increased resistant in penile arteries is impaired eNOS function combined with NO-enhanced degradation by ROS. Insufficient arteriolar sphincter and corpus cavernosum relaxation mediated by endothelium is the reason for the inability to maintain erection [24]. In addition to NO, the function of other important vasoactive agents such as the endothelin family and vasoactive prostanoids is impaired in patients with ED associated with MetS risks factors, contributing to enhanced vasoconstriction [25]. Endothelin-1 is the most powerful vasoconstricting protein synthesized in endothelial cells [26]. It contracts arterial smooth muscles and dilates them through an endothelial NO-related mechanism. This mechanism is disabled in ED. Implicating that only the vasoconstrictor effect of Endothelin-1 is present [27]. El Melegy et al. found a significantly higher plasma concentration of endothelin and angiotensin II coexisting with low levels of NO in the venous blood obtained from a man suffering from ED [28].

Regular diet mistakes among human males, such as soft drink consumption, may lead to slow and asymptomatic progression of ED, finally resulting in the full claimed manifestation of ED. It is worth to notice that impaired penile endothelial function was found in many patients without the presence of a significant peripheral endothelial dysfunction. The penile vascular bed seems to be impaired in the early stage of endothelium dysfunction. ED is a well-documented predictor of cardiovascular disease and a precursor of its manifestations [29]. Common risk factors for cardiovascular diseases are frequently found in patients with ED. On the other hand, ED is frequently reported in vascular syndromes, such as coronary artery disease (CAD), hypertension, cerebrovascular disease, peripheral arterial disease, and diabetes mellitus [30]. Endothelium dysfunction is an important risk factor to all of them.

High fructose corn syrup (HFCS)

HFCS is a major sweetener used in the soft drink industry [31]. It attracts increasing attention as the most harmful sugar component in terms of weight gain and by playing the initiating role in metabolic disorders. HFCS is more lipogenic than glucose and in high doses impairs carbohydrate metabolism, by the accumulation of fructose 2,6-bisphosphate [32]. Then HFCS leads to alterations in triglyceride and lipid metabolism thereby increasing the risk of metabolic syndrome, arteriosclerosis, and diabetes. This phenomenon is well documented in *in vivo* models [33, 34]. Soft drinks are the main source of HFCS in the human diet. Excess intake of calories and HCFS gradually leads to the deposition of fat. Visceral fat was recognized as the key risk factor for the occurrence of ED [35]. Proinflammatory molecules secreted by adipose tissue initiate chronic systemic inflammation affecting the function of the vascular system, peripheral nervous system, and hormonal milieu [36]. Dysfunction of these systems is the major pathophysiological foundation of ED. Giugliano at al. showed that all obese men with ED had higher circulating concentrations of interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-18 (IL-18), and C-reactive protein (CRP) than obese men without ED [37]. Tumor necrosis factor alpha (TNFα) is a key part of the cytokine network that governs the inflammatory response. Carencro et al. demonstrated in *in vitro* study that reduced *corpora cavernosa* smooth muscles reactivity after TNFα administration [38]. The vascular endothelium is a major target for the actions of TNFα [39]. TNFα knock-out mice exhibited increased NO-dependent relaxation, which was associated with increasing cavernosal expression of both enzymes, eNOS and nNOS [40].

Androgens and erectile dysfunction

The final effect of long-term sugar sweetened soft drink overconsumption is the development of obesity. Just seventy calories over the daily demand throughout the year results in weight gain of 8 kg. Taking the soft drink's popularity in diet, low price, and high calorie intake under consideration, soft drinks could be one of the major causes of obesity. Fat tissue secretion activities have negative impacts on the hormonal milieu that regulate male sexual functions. Kaplan et al. examined testosterone levels in 864 males and found that obese men with MetS had significantly decreased total testosterone (TT) compared to non-obese men with MetS [41]. Testosterone metabolism impairment is well documented in patients with ED. Twenty to forty percent of impotent patients characterize a reduce bioavailable testosterone (BT) level [42]. Visceral obesity is a major factor that modulates testosterone levels [43]. According to Knoblovits et al. study, BT is negatively correlated with weight circumflex (WC) [44]. Visceral fat tissue gain seems to be overwhelming on androgens metabolism and BT. Aromatase activity in adipose tissue leads to higher circulating levels of estradiol, which modulate testosterone production. In addition, the increased level of estrogens induces preferential deposition of visceral fat [45]. Adipokinesis leads to cytokine mediated inhibition of SHBG (sex hormone binding globulin) synthesis in the liver and interferes with LH/hCG-stimulated androgen secretion [46, 47]. A decrease of SHBG level is observed in obese patients and corresponds to visceral obesity whereas subcutaneous fat tissue causes testosterone level fluctuation mainly by adipocyte aromatase [48, 49].

Penile function depends on testosterone level. In penile tissue, the action of testosterone is mediated via its conversion into 5α-DHT (dihydrotestosterone) by the enzyme 5α-reductase [50]. Androgens control intracavernosal pressure by acting on corpus cavernosum muscles and vasomotor equilibrium during erection [51]. Testosterone induces NO synthesis in endothelial cells and also regulates erectile function locally by acting on the smooth muscle potassium channel within the human *corpus cavernosum* [52]. According to Trash et al., testosterone is also responsible for proper penile tissue composition. A low testosterone level initiates differentiation of progenitor stromal cells of the *corpus cavernosum* into adipogenic lineages, producing fat-containing cells and altering erectile function [53]. Androgens deficiency causes structural disorders in the *corpus cavernosum* and *tunica albuginea*, resulting in venous leakage and erectile dysfunction [54]. Veno-occlusion is modulated by the tone of the vascular smooth muscle of the resistance arteries and the cavernosal tissue and a balance between trabecular smooth muscle content and connective tissue matrix [55]. Androgens determine the fibroelastic properties of penile tissue especially the most essential for erection, the *corpus cavernosus* and *tunica albuginea*. *Tunica albuginea*, in the presence of lower androgen levels, increases thickness and loses proper arrangement of collagen fibers. Collagen bundles become diminished, are arranged irregularly, and lose their undulations [56]. The most common alterations linked to low testosterone level in the *corpus cavernosum* are smooth muscles atrophy and the accumulation of extracellular matrix, especially collagen fibrils, that in some cases even leads to fibrosis of the *corpus cavernosum*. NO- dependent relaxation of *corpus cavernosum* smooth muscles is impaired because of decreased expression and enzymatic activity of nitric oxide synthases (eNOS and nNOS) and phosphodiesterase type 5-(PDE5) [57].

Low testosterone level related changes are associated with cell cycle disorders in *corpus cavernosum* smooth muscles cells and endothelium cells of penile vessels. Testosterone is involved in penile

tissue cell apoptosis through protein p53, which is increased in low testosterone levels in males [58]. Thus androgens deficiency may escalate endothelial and erectile dysfunction manifestation.

The male behavior strictly depends on testosterone level. Burris et al. showed that men with decreased testosterone blood concentration had higher levels of depression, anger, fatigue, and confusion than men with acceptable testosterone levels [59]. We assume that soft drink consumption may be higher in this population because the craving for sweet rewards is increased by depressed mood [60]. Soft drinks, due to high sucrose dose, are excellent addictive sweets. The reward feeling after sweet soft drink consumption is mediated by endogenous opioids in the nucleus accumbens shell, which correspond to glucose blood level [61, 62].

CONCLUSIONS

Erectile function is a complex of neurovascular physiological processes that depend on the interplay among neural, vascular, hormonal, and psychological factors, as well as the integrity of the vascular bed of the penis. Soft drink related disorders may disturb all these physiological foundations of proper erection. Visceral fat deposition seems to be superior to all disorders and is the main bridge between high soft drink consumption and erectile dysfunction. In light of the facts presented in this paper, high soft drink consumption should be included in constitutive erectile dysfunction risk factors. An important question relating the influence of environmental factors on ED development may be: Do all symptoms and disorders occurring in men during ageing (diabetes type 2, hypertension, hypercholesterolemia, ischemic heart disease, cardiac failure, and MetS) have an influence on ED? Because we have a positive answer, we have to ask: Can bad nutritional habits be regarded as a triggering factor to the above-mentioned disorders? Evidence supports this suspicion can be sustained. The highest rates of obesity and diabetes are among people with low level of income, who used energy-dense food as the best way to provide daily calories. Obesity is the toxic consequence of economic insecurity and a failing economic environment. Obesity and obesity-related disorders, are epidemic in Western countries, where cheap energy-dense food can be "found", but not in really poor countries. Soft drinks are often a main course in such cheap energy menus [63-66]. On the other side, replacing sugar-sweetened beverages intake with water is associated with reductions in total calories and weight loss [67, 68].

Is there a link between soft drinks and ED? Based on their popularity and its influence on metabolism we think that the probability of such a coincidence is very high. To get a statistical proof of hypothesis a large and long-term study is needed. The most difficult is to construct such a long-term study in men. Studies on animal models can be substantially shorter. It was proven on animal models that Coca-Cola had a destructive influence on rat homeostasis, but can we replace a long-term metabolic study in men with an animal model? [69]. This is yet to be an answered question.

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