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Contributions of Increased Dietary Linoleic Acid and Fructose to the Metabolic Syndrome

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Abstract

Modern diets are characterized by an increase in fructose consumption largely facilitated by the propagation of high fructose corn syrup and the increased usage of all caloric sweeteners in a growing variety of food products. Accordingly, the human diet has seen a large increase in linoleic acid consumption over the last several decades, primarily coming from seed oils especially soybean and canola oil. It follows that the modern diet differs from the diet that was selected for by evolution and it has been suggested that the modern diet has contributed to the increased prevalence of chronic diseases currently observed. Fructose, once only found primarily in fruits, is now widely available and consumed to great excess. It is distinct from other sugars in the way it is absorbed, processed and metabolized. High levels of fructose intake have been correlated with various conditions of the metabolic syndrome, including hyperuricemia, hyperinsulinemia, hypertension, insulin resistance, leptin resistance, obesity and dyslipidemia. Likewise, linoleic acid consumption has increased with the advent of the industrial age. Modern industrial societies consume as much as 20:1 n to 6:n-3, whereas the consumption ratio of our Paleolithic ancestors has been predicted to be as low as 1:1. Radical change in our EFA profile has been associated with increased levels of atherosclerotic oxidized LDL-C and hypoadiponectinemia, which has been shown to be a strong indicator of metabolic syndrome. The studies covered in this review suggest that straying from the evolutionary selected diet has contributed to the increased prevalence of metabolic syndrome in industrialized societies worldwide. Accordingly a comprehensive effort would be advised, to restore the diet to that which humans were evolved to consume. This may suggest limiting fructose consumption to that found from natural sources and limiting linoleic acid consumption by avoiding overconsumption of seed oils for example.

Keywords: Linoleic acid; Obesity; Metabolic syndrome; Paleolithic diet; Fructose; Hypertension; Insulin resistance

Introduction

Modern day humans live in an environment extremely different from that inhabited by our ancestors of the Paleolithic age over forty thousand years ago. With the development of agricultural methods over ten thousand years ago, humans have discovered new ways to process and extract foods, increasing the variety and composition of their diet in the process. However, our genes have not changed, recording at most perhaps a 0.005% change and staying essentially similar to the genes of our ancestors of the Paleolithic age. As a consequence, there has been little time for humans to adapt to a new nutritional environment [1]. With an exponentially growth in the world population, humans have been pressured to develop fast, easy and economic methods of providing sustenance. This general review outlines some of the ways that fructose and linoleic acid have contributed to the modulation of the metabolic syndrome from an evolutionary perspective. Most recently, the machinery of the industrial age has facilitated the growth of agricultural products and these new products have been introduced into the diet of the population. Plant and seed based products, now cheaper to produce, have replaced animal based products in many parts of the diet of an industrialized society. Subsequently, the apparent dietary characteristics of industrialized civilizations are (1) an increase in total caloric consumption and a decrease in energy expenditure, (2)an increase in the consumption of saturated fat, omega-6 fatty acids and a decrease in omega-3 fatty acids, (3)a decrease in complex carbohydrates and fiber, (4) an increase in the consumption of cereal grains and a decrease in the consumption of fruits and vegetables, (5) a decrease in the consumption of protein, antioxidants and calcium and (6)an increase in the consumption of sucrose-sweetened juices, soft drinks, foods and desserts[1]. Although the changes in the human diet have not caused reproductive restriction in the species, there is evidence that the modern diet has contributed to a higher incidence of several diseases including atherosclerosis, type II diabetes, arthritis, hypertension and certain epithelial cancers [1]. An American Heart Association [2] scientific statement has reviewed the pivotal role of triglyceridesin lipid metabolism and reaffirmed that although triglyceride was not directly atherogenic, it nevertheless represented an important biomarker of CVD risk because of its association with atherogenicremnant particles and apo CIII.

This review will begin by investigating the coincident increases of fructose and linoleic acid consumption with the increased incidence of the metabolic syndrome. The review will then proceed to describe the metabolism of fructose and linoleic acid and reveal how those have contributed to the rising rates of metabolic disease, noting the negative effects of new diet trends.

Coincidence of Modern-Age Dietary Trends with the Metabolic Syndrome

Increase in fructose consumption

Fructose is a single sugar monosaccharide found naturally and almost exclusively in fruits. It is also commonly found in the disaccharide sucrose (table sugar) in a 50:50 combination with glucose, another monosaccharide. Alternatively, fructose is contained in corn-based, high-fructose corn syrup (HFCS), which contains

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varying degrees of fructose concentrations, most often around 55% concentration. Since its discovery in 1957 Japan HFCS has increasingly been used as a replacement to sucrose in processed foods and beverages such as jams, jellies, dairy products, baked desserts, cereals, canned fruits, candies, juices, sodas and sports drinks [3]. Of these products, sweetened beverages comprise nearly two-thirds of consumed HFCS in the United States. The substitution of HFCS for sucrose by manufacturers may be explained by its several advantages in marketing and production. These include a significantly sweeter taste, reduced cost and increased shelf-life [3]. HFCS has accordingly become a significant source of dietary fructose in the modern diet. Marked increases in HFCS consumption began in 1970. At this time HFCS represented less than 1% of caloric sweeteners available for consumption in the United States. Three decades later, in 2000, HFCS represented 61.2% of caloric sweeteners available for consumption [3]. This increase in HFCS availability is not perceived as a substitution of sucrose in products, but rather as an addition to the overall fructose in the diet. Data from the United States Department of Agriculture indicate that annual per capita sucrose consumption has increased from 73 lbs to 95 lbs in the same time frame that HFCS annual per capita consumption rose from <1lb to nearly 50lbs [4]. Apart from HFCS, fructose consumption from all sources has seen significant growth in the 20th century. The average per capita consumption of fructose from natural sources of fruits and vegetables is estimated to be 15gm/day [4]. Prior to World War II fructose consumption had grown slightly to 16-24g/day [4]. Decades later, a 1977-1978 USDA Nationwide Food Consumption Survey found fructose consumption to be 37g/day (8% of caloric intake) [4]. At this time HFCS began to penetrate the markets of modern societies and fructose consumption shot up to 54.7 gm/day (10.2g% of caloric intake) by 1994 as judged by NHANES III data [4]. BY 1998, fructose consumption had reached 76g/day, representing 11.5 % of caloric intake [3].

Increase in linoleic acid consumption

Linoleic acid (LA) is an omega-6 fatty acid (n-6) and one of two essential fatty acids (EFA); the other being alpha-linoleic acid (ALA) and omega-3 fatty acid (n-3). These are each characterized by the location of their first double bond counting from the methyl end of the fatty acid molecule. Therefore, the characteristic double bond of LA is found between its 6th and 7th carbon atoms, whereas the double bond of ALA is found between its 3rd and 4th carbon atoms [5]. Their classifications as "essential" fatty acids are due to the fact that they are not produced by the body and therefore must be attained in the diet. LA is naturally found mostly in the seeds of plants, while ALA is contained in the leaf components of vegetables [5]. LA and ALA are both termed short chain polyunsaturated fatty acids (SC-PUFA) and when metabolized, convert to longer desaturated long chain polyunsaturated fatty acids (LC-PUFA). Humans metabolize LA by converting it to arachadonic acid (AA), gamma-linolenic acid (GLA) and dihomo-gammalinolenic acid (DGLA. On the other hand, ALA is converted to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [6]. These LC-PUFA's have significant physiological importance and have been implicated in several disease states including psychiatric disease, cardiovascular disease and neurodevelopmental deficits [7]. As diet is the only source of ALA and LA, maintaining a diet to obtain optimal levels of these precursors and their subsequent metabolites is essential to achieving ideal health outcomes.

It is suspected that since the Paleolithic age and the dawn of the agricultural development, increased seed based product consumption has skewed the evolutionarily established fatty acid profile**.** Blasbalg et al. [7] conducted an analysis of trends in EFA consumption and human tissue content ranging from 1909 to 1999 in the United States. They used food-availability data from the Economic Research Service of the USDA and identified three hundred seventy-three different foods as sources of fatty acids. They calculated annual per capita consumption accounting for industrial usage, seed and feed usage, year-end inventories, processing, spoilage and waste. Their findings were that between 1909 and 1999 the estimated per capita consumption of butter and lard decreased by over 70%, while consumption of margarine, shortening and beef tallow increased (1038%, 170% and 371% respectively). The most significant increases in fat consumption came from soybean oil, which increased from.009kg in 1909 to 11.64kg in 1999 (well over 1000 fold increase) and rose from.006% of caloric intake in 1909 to becoming the fourth major contributor of food calories at 7.38% of caloric intake in 1999. The study also confirmed an increase in sugar consumption, noting that it had outpaced dairy consumption starting in 1972. With regards to the trends of specific fatty acid content in consumed foods, the ratio for total n-6 : n-3 increased significantly from 6.7 in 1909 to 9.6 in 1999 (a 42% increase). The large increase in soybean oil consumption is noted as the major contributor to this ratio increase.

Increase in the prevalence of the metabolic syndrome

Over the last several centuries and particularly the twentieth century, the human diet has dramatically changed. Our modern diet has rapidly outpaced the ability of our genes to adapt to our new dietary environment and thus, there has been an observed increase in several of the conditions that when co-occurring, are associated with metabolic syndrome (MetS). The World Health Organization (WHO) released a report in 1998 describing the criteria for diagnosingMetS. MetS, as defined by the WHO is characterized by: (1) diabetes mellitus, impaired fasting glucose, impaired glucose tolerance, or insulin resistance (2) two of the following: (a) Hypertension: Blood pressure (BP)≥140/90 mmHg (b) Dyslipidemia: Triglycerides (TG) ≥1.695 mmol/L and high-density lipoprotein cholesterol (HDL-C) ≥ 0.9mmol/L (male) and HDL-C ≥ 1.0mmol/L (female) (c) Central Obesity: Body mass index (BMI) ≥ 30kg/m^2 or waist : hip ratio ≥ 0.90 (male); ≥.85 (female). (d) Microalbuminuria: urinary albumin excretion ratio ≥ 20 µg/min or albumin: creatine: ratio ≥ 30mg/g [8]. The diagnosis of MetS is used to indicate a large increase in the risk for cardiovascular disease (CVD) and diabetes mellitus type II (DMII). Risk factors associated with the development of MetS include aging, rheumatic disease, diabetes mellitus, coronary heart disease, physical inactivity, stress, obesity, lipodystrophy and schizophrenia [9]. The first noted instances of MetS date back to around 1920, yet MetS has only been commonly referred to in diagnoses since 1970. Accordingly, attempts to track the progression of MetS over the century have been difficult. Ford et al. [10] conducted a study to track recent prevalence trends of MetS using NHANES data from 1988-1994 to 1999-2000. The diagnosis of MetS was identified by the presence of three of the following five criteria: (1) Central Obesity: waist circumference >102 cm (male); > 88 (female), (2) Hypertriglyceridemia: TG 1.695 mmol/L. (3) Low HDL-C: <1.036mmol/L (male); <1.295 mmol/L (female), (4) Hypertension: Blood pressure ≥ 130/85mmHg, (5) High Fasting Glucose: Glucose ≥ 5.6 mmol/L. The study revealed a significant increase in the incidence of MetS between these two time periods for those 20 years of age and older, marked at approximately 50 million cases in 1990 compared to approximately 64 million cases in 2000 (a 28% increase). The increase was particularly salient among women. Most evident was an increase in MetS among those without DMII. This increase was attributed mostly to amplified prevalence of obesity and hypertension (HTN), while

hypertriglyceridemia and low HDL-C also accounted for the increase in MetS. Central obesity in the overall population was attributed as the major contributor to MetS as prevalence rose from 22.9% to 30.5% in the U.S. from 1990-2000. It is suggested that obesity is the major contributor to MetS and that comprehensive efforts to reduce obesity may be an affective measure to reduce cases of MetS and its affiliated disease states.

Processing of Fructose and Linoleic Acid and Their Contributions to the Metabolic Syndrome

Fructose

Fructose, insulin and leptin: Fructose is absorbed in the duodenum and jejunum by a sodium independent process whereby it enters the portal circulation. Once in circulation, fructose is transported to the liver to be converted to glucose, or passes into the general circulation [3]. Fructose transported to the liver may increase de novo lipogenic processes in the liver compared to glucose, which suggests a different metabolic process from glucose [3]. Additionally, fructose does not stimulate insulin release from the pancreas, because the pancreas lacks the Glut-5 transporter for fructose [11]. Insulin signals the secretion of the hormone leptin from adipocytes, which has been demonstrated to inhibit food intake [12]. Accordingly, because pancreatic insulin secretion is not sensitive to fructose, the ingestion of fructose may contribute to over eating and obesity and may be a contributor to the metabolic syndrome [13].

Fructose increases de novo lipogenesis: The process of fructose metabolism, once fructose is transported into the liver cell by an insulin independent process via a Glut-5 transporter is distinct from the metabolism of glucose and may contribute to metabolic syndrome. Once in the cell, fructose is phosphorylated to frucstose-1-phosphate and then is cleaved by aldolase to form precursors for TG synthesis [14]. Bantle et al. [15] found that plasma TG levels increased significantly in men, but not women, who were fed a diet containing 32% fructose compared to 17% fructose. Hypertriglyceridemia has been identified as a characteristic marker of metabolic syndrome and thus overconsumption of fructose may contribute to metabolic syndrome by this contribution.

Fructose causes hyperuricemia: The metabolism of fructose in the hepatocyte has been shown to result in production of uric acid. As fructose is phosphorylated to fructose-1-phosphate, an ATP is converted to ADP and then to AMP, which results in the generation of uric acid [16]. Hyperuricemia is observed as prevalent among humans with metabolic syndrome and is thought to exacerbate the metabolic syndrome by causing endothelial dysfunction and hypertension. Nakagawa et al. [16] demonstrated that fructose–induced metabolic syndrome was significantly improved by administering allopurinol, a drug used to treat hyperuricemia. The fructose-fed rats demonstrated hyperinsulinemia, hypertension, hyperuricemia, increased body weight and hypertriglyceridemia. All of these affects were reversed by the administration of allopurinol. The study concludes that overconsumption of fructose may contribute significantly to metabolic syndrome by its affect on uric acid production.

Linoleic acid

Linoleic acid promotes oxidation of LDL-C: The risk of atherosclerosis is thought to be increased by a high level of oxidized LDL-C. Once oxidized, LDL-C particles are recognized by scavenger receptors expressed on the surface of macrophages and the LDL-C is consumed to form a foam cell on the vessel wall [17]. The foam cell secretes inflammatory cytokines, promoting the formation of atherosclerotic plaque [17]. It has been demonstrated that LA consumption in the diet leads to higher LA content within LDL-C particles, causing them to be more susceptible to oxidation [18]. This effect is especially pronounced in small dense LDL-C particles, which are thought to be primarily responsible for atherosclerotic plaque formation [18].

n-6: n-3 ratio, adiponectin and the metabolic syndrome

ALA (n-3) and LA (n-6) are both 18-carbon essential fatty acids and must be converted to their 20-carbon and 22-carbon forms in order to be biologically active. As mentioned previously, ALA is primarily converted to DHA and EPA, while LA is primarily converted to AA [19]. Each of these conversion pathways shares the same set of enzymes and therefore the ALA and LA precursors compete to be converted into their active forms. Additionally, it has been established that once converted, the n-6 and n-3 fatty acid products cannot interconvert. The action of n-3 fatty acids are generally deemed as anti-inflammatory while the actions of n-6 fatty acids are generally pro-inflammatory, yet also essential for proper function [19]. Given that both EFA's share a common metabolic pathway, which they compete for, it is essential to maintain an appropriate n-6:n-3 ratio according to our evolutionarily established set point, in order to maintain proper health. As previously described, the n-6: n-3 ratio has sharply increased in a short enough time, such that human genes could not have possibly adapted to the new dietary intake of EFA's. Recent research has sought to analyze the effects of our new n-6: n-3 ratio on health and more research is warranted on this topic. It has been suggested that reducing the n-6:n-3 ratio from levels found in the modern-diet will increase the levels of adiponectin. Adiponectin is a protein hormone found abundantly in adipose tissue and is thought to improve insulin sensitivity and inhibit vascular inflammation by interfering with the action of tumor necrosis factor-α (TNA-α) on endothelial cells [20]. Guebre-Egziabher et al. [21] conducted an intervention study where an experimental group of 17 subjects reduced their n-6:n-3 ratio intake to 2.2 from 32.2. These subjects were shown to have a significant increase in adiponectin and fatty oxidation and a significant decrease in glucose oxidation rate in LDL-C and TNF-α. As the function of adiponectin is integral to glucose homeostasis, adiponectin deficiency is suspected to be a contributor to the development of metabolic syndrome. Renaldi et al. [20] conducted a study comparing adiponectin levels in 40 individuals with metabolic syndrome to those in 40 individuals without metabolic syndrome. Those included in the study were between the ages of 22 and 55 and metabolic syndrome was diagnosed by a waist circumference > 90cm (male); > 80cm (female) and 2 of the following criteria: (1) Hypertriglyceridemia: TG > 150 mg/dL (1.7 mmol/L) (2) Low HDL-C: HDL<0.9 mmol/L (male); < 1.29mmol/L (female) (3) Hypertension: Blood pressure > 130/85 mmHg (4) Increased fasting glucose: fasting glucose > 5.6 mmol/L. The study concluded that those diagnosed with metabolic syndrome were six times more likely to have hypoadiponectinemia and 5.7 times more likely to be insulin resistant than subjects without metabolic syndrome. Interestingly, variations have been noted in the rate of development of the metabolic syndrome, some related to genotype. For example, Gong et al. [22] have found that genetic variation in the Stearoyl-CoA Desaturase 1 (SCD1) gene may play a role in the development of the metabolic syndrome. SCDI is indeed a key regulator of lipid metabolism. As well, Duan et al. [23] have shown significant genetic contributions to the sub-phenotypes of the metabolic syndrome. They purport that although pleiotropic genetic control may exist for some physiologically similar phenotypes, their results do not support a common genetic mechanism among the

phenotypes that they observed in their twin-based heritability study in the Chinese population.

Conclusion

Modern diets are characterized by an increase in fructose consumption largely facilitated by the propagation of high fructose corn syrup and the increased usage of all caloric sweeteners in a growing variety of food products. Similarly, the human diet has seen a large increase in linoleic acid consumption over the last several decades, primarily coming from seed oils especially soybean and canola oil. It follows that the modern diet differs from the diet that was selected for by evolution and it has been suggested that the modern diet has contributed to a variety of chronic diseases. Fructose, once only found primarily in fruits, is now widely available and consumed to great excess. It is distinct from other sugars in the way it is absorbed, processed and metabolized. High levels of fructose intake have been correlated with various conditions of the metabolic syndrome including hyperuricemia, hyperinsulinemia, hypertension, insulin resistance, leptin resistance, obesity and dyslipidemia. Likewise, linoleic acid consumption has increased with the advent of the industrial age. Modern industrial societies consume as much as 20:1 n-6: n-3, whereas the consumption ratio of our Paleolithic ancestors has been predicted to be as low as 1:1. Radical change in our EFA profile has been associated with increased levels of atherosclerotic oxidized LDL-C and hypoadiponectinemia, which has been shown to be a strong indicator of the metabolic syndrome. The studies covered in this review suggest that straying from the evolutionary selected diet has contributed to the increased prevalence of metabolic syndrome in industrialized societies worldwide. Some variations by phenotype have been noted that warrant further study. It remains that given the epidemiology of the metabolic syndrome, the findings summarized in this review and the position statement of the American Heart Association and others, a comprehensive effort is warranted, in order to restore the diet to that which humans have evolved to consume. This would imply limiting fructose consumption to that found in natural sources and limiting linoleic acid consumption by avoiding overconsumption of seed oils. Further studies should explore the trends in associated morbidities, such as visceral adiposity, obesity and dyslipidemia. In addition, further discussions should include the relevant dose-dependence of the negative metabolic effect and finally, the impact of gender, race and age on fructose metabolic effects.

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