Nutrition 30 (2014) 1–9

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

Today's and yesterday's of pathophysiology: Biochemistry of metabolic syndrome and animal models

Suleyman Aydin Ph.D. [a,*], Aziz Aksoy Ph.D. [a,b], Suna Aydin M.D. [c,d], Mehmet Kalayci M.D. [a], Musa Yilmaz M.D. [a], Tuncay Kuloglu M.D. [f], Cihan Citil Ph.D. [a,e], Zekiye Catak M.D. [a]

[a] Department of Medical Biochemistry and Clinical Biochemistry (Firat Hormones Research Group), Medical Faculty, Firat University, Elazig, Turkey
[b] Department of Nutrition and Dietetics, Bitlis Eren University, Bitlis, Turkey
[c] Department of Anatomy, Medical Faculty, Firat University, Elazig, Turkey
[d] Department of Cardiovascular Surgery, Elazig State Hospital, Elazig, Turkey
[e] Department of Biological Science (Biochemistry Section), Firat University, Elazig, Turkey
[f] Department of Histology and Embryology, Medical Faculty, Firat University, Elazig, Turkey

ARTICLE INFO

Article history:
Received 11 December 2012
Accepted 23 May 2013

Keywords:
Metabolic syndrome
Fructose mechanism
Experimental animal models
Biochemistry

ABSTRACT

During the past 20 y, there has been much interest in sugars and especially fructose in relation to human health. Over the past decade, considerable scientific debate and controversy have arisen about the potential health effects of sucrose, high-fructose corn syrup (HFCS), and fructose itself. HFCS increasingly has been used as a sweetener in thousands of food products and soft drinks, leading to the development of obesity, diabetes, dyslipidemia, and metabolic syndrome (MetS) in both rodents and humans, which is associated with an increase in body weight. There is a need for detailed research on the mechanism underlying MetS that could lead to a remedy. This review will first systematically present a definition of MetS, its history, prevalence, and comparative diagnostic criteria. We will then consider fructose and its effects on human health, the diet-induced obesity model (various fat contents), the hypercholesterolemic model, the diabetes model, the hypertensive model, the MetS or insulin resistance model, and biomarkers related to MetS, in light of contemporary data using multiple databases (PubMed, MEDLINE, and OVID).

Introduction

In recent years, much attention has been given to metabolic syndrome (MetS) owing to its role in the development of diseases such as obesity, diabetes, and cardiovascular disease (CVD). The pathogenesis of MetS is complex and the underlying mechanisms are not clearly understood [1]. To elucidate these mechanisms, many experimental animal models have been used. This review focuses on the definition, history, prevalence, and diagnostic criteria of MetS, and the physiological and biochemical events involved, in human and animal studies. The causes and experimental animal models used to shed light on the etiopathology of MetS are reviewed, and the effects of additional dietary fructose are discussed; a brief summary is appended.

Metabolic syndrome

MetS is also called insulin resistance syndrome, syndrome X, polymetabolic syndrome, deadly quartet, and civilization syndrome. It is a grave public health problem and is becoming increasingly widespread throughout the world. The syndrome, which involves all biological systems, causes high morbidity and mortality because of its cardiac and metabolic complications [2–6]. Believed to result from the interaction of genetic and environmental factors, MetS comprises a combination of cardiometabolic risk factors including abdominal obesity, insulin resistance, glucose intolerance, dyslipidemia, non-alcoholic fatty liver (NAFL), and hypertension [2–5,7]

Currently, the most commonly used set of criteria is the one established by the World Health Organization (WHO) in 1988. According to WHO, the diagnosis of MetS requires the presence of diabetes, impaired fasting glucose, impaired glucose tolerance, or insulin resistance, together with at least two of the following: hypertension (>130/85 mm Hg), hyperlipidemia, central obesity, and microalbuminuria [5]. The U.S. Expert Panel

* Corresponding author. Tel.: +90-533-493-4643; fax: +90-424- 237-9138.
E-mail address: saydin1@firat.edu.tr (S. Aydin).

0899-9007/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.nut.2013.05.013

of the National Cholesterol Education Program (NCEP) prepared a report on the detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III [ATP III]). Of the criteria proposed for defining MetS, the most commonly used are those in ATP III. The co-presence of at least three of the ATP III criteria (obesity: waist circumference ≥102 cm in men and ≥88 cm in women; dyslipidemia: triglyceride [TG] 150 mL/dL and/or high-density lipoprotein cholesterol [HDL-C] ≤ 40 mg/dL in men and ≤50 mg/dL in women; blood pressure: ≥130/85 mm Hg; and glucose: ≥110 mg/dL; and diabetes mellitus) is considered diagnostic for MetS. The diagnostic criteria for MetS have not yet been standardized; currently, however, ATP III criteria are used in many clinics [5–12]. Various other versions of MetS diagnostic criteria have been proposed by other study groups (such as the American Association of Endocrinologists [AACE], European Group for the Study of Insulin Resistance [EGIR], American Heart Association/National Heart, Lung, and Blood Institute [AHA/NHLBI], Turkish Association of Endocrinology and Metabolism [TEMD]; etc.) and can be used in clinical practice [5,8,9].

The term "metabolic syndrome" and the history of MetS

MetS was first defined in 1923 as "The co-presence of hypertension, hyperglycemia and gout." It was reported in the late 1940s to be associated with central obesity, diabetes, and atherosclerosis, and gout [13]. At the 1965 annual meeting of the European Association for the Study of Diabetes (ESAD), MetS was reported to be a syndrome consisting of hypertension, hyperglycemia, and obesity [14]. In the 1970s, German researchers used the term *metabolic syndrome* for the first time and they explored its relationship to atherosclerosis. In 1988, Raeven suggested the name *Syndrome X* for this group of cardiovascular risk factors, which include hypertension, glucose tolerance, high TG levels and low HDL-C [15]. It also was stated that insulin resistance and compensatory hyperinsulinemia constituted the main mechanism underlying MetS and that Syndrome X was a serious risk factor for CVDs [16]. MetS also has other synonyms including dysmetabolic syndrome, plurimetabolic syndrome, cardiometabolic syndrome, dyslipidemic syndrome, prediabetes, dyslipidemic hypertension, and hypertriglyceridemic waist [5,17]. Numerous clinical conditions such as hypertension; dyslipidemia, NAFL disease; polycystic ovary syndrome (PCOS); sleep apnea syndrome (SAS), Alzheimer's disease, and lung, prostate, and pancreatic cancers have been accepted as clinical manifestations of this syndrome [5,18–20].

The prevalence of metabolic syndrome

Because no single definition of metabolic syndrome has gained worldwide acceptance, data regarding its prevalence vary. In a Finnish study that registered individuals in the 24 to 39 y age range, MetS prevalence was found in 9.8% of individuals according to EGIR criteria and 14.3% according to the International Diabetes Federation (IDF) criteria [21]. The results of The National Health and Nutrition Examination Survey III (NHANES III) conducted between 1988 and 1994 on adults older than age 20 y in the United States showed that the prevalence of MetS was 23.9% according to the NCEP ATP III) criteria and 25.1% according to the WHO criteria [10–12,22–24].

According to the NCEP ATP III criteria, the prevalence of MetS ranged from 5.6% in Chinese women [25] to 52.8% in Polynesian men in New Zealand [26]. Women showed a higher prevalence of MetS than men among Africans, Arabs, Iranians, Mexicans, and South Asians [27], but a lower prevalence among whites and Hispanics [20]. Among 9846 Iranian individuals over the age of 20 y, the prevalence of MetS was 24% and 42% in men and women, respectively [28].

The Survey of the Prevalence of Heart Disease and Risk Factors among Turkish Adults (TEKHARF) [29] using the NCEP ATP III criteria revealed an MetS prevalence of 28% among men and 45% among women of at least 30 y of age. It is estimated that 9.1 million adults (of whom 5.1 million are women) over the age of 30 in Turkey have MetS [10,11]. The prevalence of MetS was 24.4% in 1990 and increased to 36.2% in 2000 [30]. The results of another 2004 study titled "Research on the Prevalence of Metabolic Syndrome in Turkey (METSAR)" established that the prevalence of MetS was 35% among adults over the age of 20. That study revealed that MetS was more prevalent in women [2,31] than men (28.8%) [32]. A 2006 study that investigated MetS and associated disorders in Turkey [33] established MetS prevalences of 10% in men and 27% in women.

Etiology of metabolic syndrome

The factors that are most commonly blamed in the development of MetS are insulin resistance and obesity [3–5,34]. In cases of insulin resistance in MetS, the pathology is at the post-receptor level; it develops as a result of disorders in the intracellular pathways after insulin binding to its receptor. Obesity, a sedentary lifestyle, smoking, low birth weight, and perinatal malnutrition are all associated with the development of insulin resistance. Other factors in the development of insulin resistance include hormones secreted from adipose tissue, hypothalamus–hypophysis–adrenal axis disorders, and excessive accumulation of fat, as well as genetic and environmental factors [35]. Insulin resistance plays a critical role in the pathologies constituting MetS such as dyslipidemia, hyperglycemia, hypertension, and obesity [7,36].

Although obesity is considered the main component in the development of MetS, not all obese individuals suffer from an impaired metabolic profile or insulin resistance [16,18,37]. Studies involving different ethnic groups have demonstrated different phenotypes of MetS in individuals with insulin resistance. This led to an exploration of the effects of genetic heritage. A study of a population in which insulin resistance was common provided an example: the prevalence of type 2 diabetes was elevated, but there was no such increase in the prevalence of hyperlipidemia or hypertension [16,18,38]. Abdominal or visceral obesity was reported to be associated with hyperinsulinemia, insulin resistance, increased free fatty acid levels, hypertension, predisposition to thrombosis, and a decrease in hypertriglyceridemia, as well as small-density low-density lipoprotein (SD-LDL) particles and HDL-C [5,39].

Human studies

Consumption of high-fructose corn syrup (HFCS), which is made from corn and usually contains 42% (HFCS–42) or 55% (HFCS-55) fructose [40], has increased throughout the world, contributing to increased total caloric intake and, since its introduction in 1967, has resulted in an increase in MetS. The rise in energy drink consumption increased the likelihood of obesity, diabetes, and MetS [41].

Several studies have revealed a positive association between consumption of sweetened beverages, mainly among teenagers, and body weight [6,40,42–45]. It also has been suggested that excessive consumption of sweetened beverages with added