World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i12.3449

World J Gastroenterol 2015 March 28; 21(12): 3449-3461
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Genome-based nutrition: An intervention strategy for the prevention and treatment of obesity and nonalcoholic steatohepatitis

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Conflict-of-interest: No potential conflicts of interest relevant to this article were reported.

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Received: November 28, 2014
Peer-review started: November 28, 2014
First decision: January 8, 2015
Revised: January 21, 2015
Accepted: February 12, 2015
Article in press: February 13, 2015
Published online: March 28, 2015

Abstract

Obesity and nonalcoholic steatohepatitis are increasing in westernized countries, regardless of their geographic location. In Latin America, most countries, including Mexico, have a heterogeneous admixture genome with Amerindian, European and African ancestries. However, certain high allelic frequencies of several nutrient-related polymorphisms may have been achieved by past gene-nutrient interactions. Such interactions may have promoted the positive selection of variants adapted to regional food sources. At present, the unbalanced diet composition of the Mexicans has led the country to a 70% prevalence rate of overweightness and obesity due to substantial changes in food habits, among other factors. International guidelines and intervention strategies may not be adequate for all populations worldwide because they do not consider disparities in genetic and environmental factors, and thus there is a need for differential prevention and management strategies. Here, we provide the rationale for an intervention strategy for the prevention and management of obesity-related diseases such as non-alcoholic steatohepatitis based on a regionalized genome-based diet. The components required to design such a diet should focus on the specific ancestry of each population around the world and the convenience of consuming traditional ethnic food.

Key words: Latin America; Mexico; Gene-nutrient interactions; Evolution; Food history; Western diet; Nonalcoholic steatohepatitis; Obesity

Core tip: New intervention strategies for the prevention and management of obesity and associated gastrointestinal diseases are warranted due to their chronic complications. In the era of genomic medicine and nutritional genomics, we are now closer to understanding how unbalanced gene-nutrient interactions are involved in the onset and progression

of these diseases. The implementation of regionalized diets based on the genetic ancestry and natural staple food sources of each population may result in better health and nutrition worldwide. Further studies are required to tailor the appropriate diet for each type of population to win the battle against obesity and associated co-morbidities.

Roman S, Ojeda-Granados C, Ramos-Lopez O, Panduro A. Genome-based nutrition: An intervention strategy for the prevention and treatment of obesity and nonalcoholic steatohepatitis. *World J Gastroenterol* 2015; 21(12): 3449-3461 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i12/3449.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i12.3449

INTRODUCTION

Overweightness and obesity have been relatively accepted as the conspicuous culprit associated with the increasing incidence of metabolic-related co-morbidities[1,2]. The rate by which the prevalence of obesity has increased in the last decades has led health experts to estimate that 1.4 billion adults are overweight globally, and of these overweight adults, 300 million are obese[3]. In addition, obesity has grown markedly faster among the developing countries in a shorter time span than the developed world[4]. In consequence, regardless of whether populations are geographically located in the Eastern or Western hemisphere, populations that have rapidly adopted a westernized lifestyle are now immersed in an obesogenic environment[5]. This environment is characterized by the consumption of calorie-dense foods, reduced physical activity, and greater psychosocial stress driven by macro-level factors of globalization[6,7]. Unfortunately, as the world's adult population obesity increases, the next human generations are becoming more susceptible to gaining weight at earlier stages of life. Estimations using World Health Organization data have shown that global childhood obesity increased from 4.2% in 1990 to 6.7% in 2010[8]. Furthermore, as this trend continues to rise, the relative risk of morbidity and mortality due to premature type 2 diabetes mellitus (T2DM)[9] and cardiovascular disease (CVD)[10] is rising accordingly.

The link between obesity and the increasing prevalence of associated chronic illness is that obesity is more than an input-output energy ratio imbalance[1]. Obesity generates a highly complex multisystem deregulation of the glucose and lipoprotein metabolism orchestrated by insulin resistance invoked through an excess of serum fatty acids[11]. Insulin resistance is a key component of the metabolic syndrome that ultimately leads to cellular oxidative stress and low-grade systemic inflammation affecting several tissues and organs[12]. One such organ is the liver. Thus, the next-in-line co-morbidity after viral hepatitis and alcoholic liver disease may be non alcoholic fatty liver disease (NAFLD), which comprises fatty liver and nonalcoholic steatohepatitis (NASH)[13,14]. Unchecked, these conditions may lead to fibrosis/cirrhosis and hepatocellular carcinoma[15-17]. However, despite the similarity in the rising worldwide pattern of obesity, the myriad causal-effect relationships involved in the pathogenesis of NAFLD/NASH are not fully understood[18]. Moreover, virtually all stages of progression, from obesity to long-term complications, may be modulated by hereditary and environmental factors[11,18]. Hence, the wide variety of abnormal metabolic phenotypes derived from the obese state may be due to disparities in the population´s distribution of gene polymorphisms interacting with nutritional factors.

Currently, genomic sciences are providing us with a better understanding of how nutrients interact with the human genome and the impact of natural selection on genes involved in modern-day complex diseases[19]. Additionally, variations in the allelic frequencies of nutrient-related polymorphisms may mark the differences in risk of complex diseases among populations[20]. Moreover, human societies that have conserved their staple food diet are less prone to nutrition-related diseases[4,21]. Thus, prevention and treatment strategies for obesity-related diseases should be based on the rationale of a regionalized genome-based diet rather than a one-size-fits-all approach[5]. The components of such a diet should focus on the genetic susceptibility and the traditional food culture of each population. Thus, the aim of this editorial is to describe several gene-diet interactions that may contribute to obesity and NAFLD/NASH. We conclude with a genome-based nutrition intervention strategy that defines the best dietary resources according to the individual's background.

EVOLVING HUMAN GENOME-NUTRIENT INTERACTIONS

Evolutionary genomics has offered insights on how new climates, diet, and infectious diseases exert positive selective pressures on the human genome, especially within human subpopulations[20,22]. Hunting the genome for "signatures" of positive selection has led scientists to parts of metabolic gene sequences that evolve more rapidly than others when exposed to environmental challenges[20,23,24]. However, these adaptive challenges can occur in distinct geographic areas, rendering differences in the frequency of alleles of the single nucleotide polymorphisms (SNPs) that allow carriers to adapt to such environmental challenge[20,25,26]. Interestingly, this dynamic interaction between genes and diet also seems to be mediated by culture practice. For example, a recent discovery was the finding that the marine microbe *Zobellia*

Table 1 Allelic frequencies of nutrient-interacting genes in America and worldwide

Gene	Allele	Population	Frequency (%)	Ref.
MTHFR	677T	Huicholes (Native Mexican)	56.0	Dávalos *et al*[28] 2000
		Asian	36.7	HapMap-JPT[29]
		European	23.7	HapMap-CEU[29]
		African	11	HapMap-YRI[29]
TAS2R38	AVI	European	47	Kim *et al*[30] 2003
		Asian	30	
	PAV	Southwest Native American	100	
		Asian	70	
		European	49	
AMY1	Copy number	European-American (high starch diet)	6.8[1]	Perry *et al*[31] 2007
		Mexican (high starch diet)	6.1[1]	Mejía-Benítez *et al*[32] 2014
		Biaka African (low starch diet)	5.47[1]	Perry *et al*[31] 2007
		Yakut Asian (low starch diet)	5.24[1]	
CD36	-31118A	Egyptian	67.5	Bayoumy *et al*[33] 2012
		Caucasian	53.6	Ma *et al*[34] 2004
		African American	43.8	Keller *et al*[35] 2012
		North Indian	38.2	Banerjee *et al*[36] 2010
ABCA1	230C	Xavantes (Native Brazilian)	31	Acuña-Alonzo *et al*[37] 2010
		Coras (Native Mexican)	29	
		European	0	
		Asian	0	
		African	0	
APOE	E2	African	19	Singh *et al*[38] 2006
		European	12.7	
		Asian	4.6	
		Huicholes (Native Mexican)	0	
	E4	Huicholes (Native Mexican)	28.7	Aceves *et al*[39] 2006
		African	27	Singh *et al*[38] 2006
		Asian	10.5	
		European	1.1	
LCT	-13910T	European	39.1	Corella *et al*[40] 2010
		White Brazilian	24.7	Mattar *et al*[41] 2009
		Mapuches (Native Chilean)	22.2	Morales *et al*[42] 2011
		Black Brazilian	12	Mattar *et al*[41] 2009

[1]Mean copy number.

galactanivorans may have transferred algae-digesting enzymes to the human gut bacterium *Bacteroides plebeius*[26]. This microbe contains a B-prophyranase gene similar to one identified in the marine bacterium that breaks down algae carbohydrates, as in the food nori, which otherwise would be indigestible. However, to date, only people of Japanese ancestry, who have a legendary consumption of nori-made sushi-rolls and other algae-based foods, are gifted with this type of microbiota. Another example is the lactase persistence trait: the ability to digest fresh milk and other dairy products into adulthood is more frequent in pastoralist and dairying populations of northern Europeans and in certain African and Arabic nomadic groups, in contrast to the rest of the world[27]. Likewise, among the Latin American countries, milk was never a genetically recognized food among the Amerindians until the arrival of the Europeans.

In Table 1, several nutrient-interacting genes are depicted to illustrate their contrasting allelic frequencies worldwide, including the Americas. The methylenetetrahydrofolate reductase (*MTHFR*) enzyme involved in the one-carbon metabolism[28,29], the taste receptor 2R38 (*TAS2R38*) for the perception of bitter and pungent substances[30], amylase 1 (*AMY1*) to digest complex carbohydrates[31,32], lipid metabolism genes: Class B scavenger receptor (*CD36*)[33-36], ATP binding cassette transporter (*ABCA1*)[37] and Apolipoprotein E (*Apo E*)[38,39], and lactase (*LCT*) enzyme[40-42] all express population-based allele dominance that may define differential dietary requirements within humans[20,35,36]. Moreover, these adaptive genes that were once shaped in a specific natural environment may now become disease alleles due to the rapid shifting man-made surroundings or even recent genetic admixture of a given population[43-45]. Therefore, in the following section, we explain the genetic basis and food history common to the American population of which Mexico is representative.

AMERINDIAN ANCESTRY AND FOOD HISTORY IN LATIN AMERICA

Early years: First settlers and native food sources

The indigenous Americans descend from at least three streams of gene flow, and archaeological evidence shows that early settlers in Mexico date back to 30000

years ago[46,47]. The nomadic lifestyle of the initial ancestors and the climatic changes conditioned their southward expansion through the American continent[48]. The initiation of the food history in septentrional Latin America begins in two pre-Hispanic geographical regions with distinct ecosystems. Aridoamerica, an extraordinarily biodiverse dryland situated in the north and central region, was the home of small and isolated semi-nomadic groups living a Paleolithic lifestyle[49]. In contrast, Mesoamerica was a territory that extended from the middle region of Mexico to the northern part of Central America. It has incredible natural biodiversity, especially in the Mexican Basin, which has since early times drawn nomadic groups of hunter-gatherers to becoming sedentary societies eventually[50,51]. They were small groups of people living on a Paleolithic diet consisting of wild plants, lacustrine animals, and hunting small animals, followed by big game[50]. The adequate climatic conditions and environment of Mesoamerica allowed the first cultivation of plants (5500 BC). Finally came the emergence of agriculture and the development of the Neolithic sedentary societies (2500 BC; Pre-Classic stage)[51].

The development of several agricultural societies was the starting point of a new food chain system that allowed the consumption of a mixed diet based on cultivated plants such as maize, squash, chili, avocado, edible green leafy vegetables known as *"quelites"*, amaranth, chia and beans[45,50,51]. However, it also included turtle meat, deer, domesticated dogs and other foods obtained by fishing, hunting and gathering practice. In the following years, comprising the Classic (150-900 AC) and Post-Classic (900-1519 AC) stages, the pre-Hispanic cultures developed, grew and spread along with intensive agricultural production using the *milpa* (cornfield combined with other staple plants) and *chinampas* systems (wetland agriculture)[50,51]. Before the conquest, the most developed population was *Tenochtitlan* (the Aztec capital city). By this time, the food regime of most all the neighboring ethnic groups was mainly the pre-Hispanic diet that will be discussed in section Ⅳ. Meat was uncommon for most people, and its consumption was reserved for the "nobles" or at special ceremonies; instead, most of the population ate several species of worms, insects, and wild herbs that were a rich source of protein. These ancestors took wisely what was given by nature and turned it into peculiar tasty dishes. Furthermore, they discovered the healing powers of food, what to avoid and eat to prevent and cure diseases.

Conquest and colonial times: The initial genetic and food culture admixture

In 1519, the Spaniards arrived. The genetic and cultural admixture of the Amerindian forefathers began with the European colonization that continued from the conquest of *Tenochtitlan* in 1521 until 1851[52]. The Spaniards introduced a wide variety of crops and domestic animals that allowed them to continue their own food habits. Foodstuffs such as wheat, sugar cane, cattle, pigs, sheep, goats, chicken, radish, lettuce, cabbage, cucumber, pomegranate, pear, apple, grape, fig, peach, and oils, among others were brought[45]. Thus, the original diversity of the rich pre-Hispanic sources of nutrients was diminished due to eradication by the Spaniards of all food that was related to non-Christian religious ceremonies or unfamiliar to their taste buds. They abandoned some foods such as amaranth and chia, rich in proteins and polyunsaturated fats, yet on the other hand, a new admixture of novohispanic dishes arose.

Over time, the Amerindian population decreased due to warfare, overwork and the presence of epidemic diseases, allowing the widespread settlement of Europeans together with the almost complete imposition of their culture, followed by the arrival of slaves from several regions of Africa[52]. These three populations were the founder races that originated the genetic admixture of the early mestizos, socially known as "las castas", which prevailed during the 300 year Colonial period[45]. This time served as the cradle of the genetic and cultural differences that continue in present-day Mexico, which also occurred among other Latin American countries.

Gradual transformation of food habits

Intertwined with the early historical events of Mexico's Independence (1821) and Revolution (1921) came the gradual industrial growth from the 17th through the 18th century that brought new foreigners to Mexico. In recent years, immigration has shaped the present-day gene pool of the Mexican population[53]. Thus, genome-wide analysis has shown that the genetic architecture of the Mexican population and of most Latin American populations is a heterogeneous admixture of Amerindian, European and African ancestries[39,46,48]. However, the percentage of each ancestral component varies with region, contributing to the overall heterogeneity[39,53,54].

Mexico's food history provides an excellent setting to explore the effect caused by the interaction between ancestral genes and the native food regimen, one that might have exerted selective pressures on certain SNP's related to food metabolism. Having been positively selected, they served for survival in the ancestral environment; however, at present, they may have become detrimental. In the last five hundred years, the Mexican population has "progressed" from a society with a traditional lifestyle to a modern lifestyle along with an unfortunate nutrition transition. Thus, in the following section, we describe some examples of mismatched gene-nutrient interactions and their plausible association with metabolic liver disease.

GENETIC ADAPTATIONS FOR REGIONAL FOOD SOURCES

Vegetables

MTHFR C677T polymorphism: The Amerindian's pre-Hispanic diet was rich in a wide variety of vegetables that provided the vitamins and minerals needed to prevent nutritional deficiencies. Many indigenous foods such as maize, green beans, avocado, chia and "*quelites*" are natural sources of folates[45]. An extensively studied SNP is the *677T* allele of the *MTHFR* gene that encodes a thermolabile enzyme with decreased activity. This enzyme catalyzes the conversion of 5, 10-methylenetetrehydrofolate to 5-methyltetrahydrofolate, the most abundant form of folate in the plasma[55] and a co-substrate for homocysteine remethylation to methionine. In combination with an insufficient folate intake, it has currently been associated with neural tube defects[56], CVD[57,58], hyperhomocysteinemia, liver steatosis and NASH[59-61]. However, the abundance of folates in the Amerindian's pre-Hispanic diet could have acted as a positive selection pressure for this SNP without causing any disease in the population. Evidence of genetic selection for the T allele related to folate intake has been reported[62-64]. In regard to the Mexican population, the highest frequencies of the T/T genotype have been found among native groups with a high Amerindian ancestry compared with other world populations, as shown in Table 1.

TAS2R38 haplotypes: The ability to taste bitter substances such as the ones found in cruciferous vegetables as well as the perception of sweet taste, the pungency of chili peppers and the texture of fats varies within human populations. In this connection, studies have suggested that exposure to these food substances may have been an important factor in the evolution of this trait[65]. This ability is sustained by the genetic variability of three functional SNPs in the *TAS2R38* gene[66] that have led to the existence of two amino acid haplotypes: alanine, valine, isoleucine (AVI), and phenylalanine, alanine and valine (PAV). AVI/AVI homozygotes present the lower bitter taste sensitivity (non-tasters), whereas PAV/PAV homozygotes show the highest sensitivity to these flavors (tasters)[66,67] (Table 1). Consistently, it has been reported that AVI/AVI homozygotes consume more bitter cruciferous vegetables than either PAV/AVI heterozygotes or PAV/PAV homozygotes[68]. Therefore, being a non-taster may have significant health benefits, as bitter tasting foods such as grapefruits, coffee and cruciferous vegetables have been recognized for their antioxidant properties.

In regard to the pre-Hispanic diet, the wide variety of chili plants (Capsicum spp.) of Mesoamerica were essential ingredients of the staple diet and thus a good source of vitamins such as A and C[45]. However, the tolerance for both the pungency of capsicum, the main ¨hot¨ component of the chili plant, and for the bitter taste of the quelites may have required the presence of a non-taster phenotype. Thus, the non-tasting for quelites allows on the one hand the acquisition of adequate amounts of dietary folates, which, in conjunction with the aforementioned *MTHFR C677T* SNP, allows a proper metabolism of homocysteine and the final endogenous production of glutathione. Currently, vitamins A and C have been studied for their antioxidant properties in the treatment of liver diseases, although glutathione is a clinically significant antioxidant because low levels play an important role in the pathogenesis of NAFLD[64].

Legumes and cereals

Copy number of *AMY1* gene: Our Amerindian predecessors were creators of complex agricultural systems, nearly 7000 years ago. In the *milpa* and the *chinampas* grew many new foods, some of which contained a high content of starch, such as maize and beans[45]. Therefore, as in other agricultural societies, it may be inferred that the Mexican population is genetically adapted to diets high in complex carbohydrates. This dietary change increased the need for a higher protein levels of salivary amylase (enzyme responsible for starch hydrolysis), which has been associated with an increase in the number of copies of the gene encoding it (*AMY1*)[69] It has been hypothesized that natural selection may have influenced the variation of the *AMY1* copy number in human populations with traditionally high-starch diets, thus improving the efficiency by which these foods are digested in the gastrointestinal tract[31]. Some studies have shown that *AMY1* copy number is positively correlated with the level of amylase protein expression in saliva[68,69]. Furthermore, it was found that the mean diploid *AMY1* copy number is higher in individuals from agricultural populations with diets rich in complex carbohydrates (European-Americans and Japanese) than individuals from populations with diets including relatively few starchy foods (Datog, Mbuti and Biaka in Central-East region of Africa and the Yakut in Asia) (Table 1). *AMY1* copy number has been recently studied in the Mexican population, in which a high copy number of the *AMY1* gene may protect against obesity[32]. However, a high intake of simple carbohydrates in the diet has showed correlation with obesity and severity of fatty liver in the absence of traditional risk factors[70,71].

Fats and cholesterol

***CD36* gene:** The overconsumption of high-fat foods depends upon their high palatability and taste perception[72-75]. Class B scavenger CD36 receptor plays a fundamental role in the taste perception of dietary fat[76] by capturing long-chain fatty acids into the cell[77]. Thus, the genetic variability of the *CD36*

gene could explain the differences in fat perception and fat preferences across individuals[35] (Table 1). It has been reported that SNP *-31118G>A* in the promoter region predicts the oral responses and preference for dietary fat in adults of African-American ancestry by reducing the CD36 expression[78,79]. Positive selective pressure may have favored the A allele in the native Amerindians because the composition of their habitual diet has been low in fat, thus maintaining low levels of the CD36 receptor. However, exposure to the obesogenic environment in which the country is currently immersed could favor the consumption of high-fat foods and obesity.

ABCA1 R230C polymorphism: Foods such as avocado, squash seeds, cacao, and chia, as well as lacustrine resources and the lean meat of certain animal species were the staple fat sources from our ancestors' diet[45]. These sources were characterized primarily by providing polyunsaturated fatty acids and low amounts of saturated fat and cholesterol[37]. ABCA1 is the major transmembrane transporter that mediates the efflux of cholesterol and phospholipids from cells to apolipoprotein A-Ⅰ (apoA-Ⅰ) to generate nascent HDL particles[80]. Thus, the liver not only participates in synthesizing these nascent HDL particles, which are transported to the periphery for reverse cholesterol transport, but also serves as a source of cholesterol for plasma HDL acceptors (including ovary, adrenal and testis tissues). Therefore, the liver and peripheral cells modulate the intracellular level of cholesterol by the level of expression of the ABCA1 transporter[81].

However, the non-synonymous variant *R230C* of the *ABCA1* gene has been associated with low HDL cholesterol levels because it reduces the cholesterol efflux by 27%. Interestingly, this variant has shown evidence of recent positive selection in Native-Americans, given that it has been found to be exclusive to Native American and Native American-derived populations. It has been speculated that *230C* carriers could have had a selective advantage, due to a lower cholesterol efflux, that could favor the storage of intracellular cholesterol and energy to survive periods of famine and adapt to low-fat diets. However, under current westernized lifestyle changes, the *230C* allele may represent a disadvantage for low HDL cholesterol levels (hypoalphalipoproteinemia), indeed one of the most common dyslipidemia in Mexicans[37]. Moreover, this variant has also been associated with higher body mass index and NAFLD[82].

Apo E polymorphism: The *Apo E* gene encodes a plasma glycoprotein that is part of the structure of triglyceride-rich lipoprotein (VLDL, HDL, chylomicrons). Thus, Apo E protein mediates their metabolism in the liver and acts as a ligand for low-density lipoprotein (LDL) receptors. Three alleles (*E2*, *E3*, and *E4*) determine six genotypes with well-described amino acid substitutions at positions 112 and 158[83]. Such substitutions confer differential binding affinities for their respective receptors. *Apo E3* allele is the most frequent isoform that allows the proper binding of Apo E-containing lipoproteins to their receptors (E/B, rLDL)[83]. However, the *E2* isoform binds defectively to the LDL receptors, whereas the *E4* isoform has a higher affinity for triglyceride-rich lipoproteins that increases the liver uptake of these lipoproteins; consequently, LDL receptors are down-regulated[83,84]. Apo *E4/E4*, *E4/E2* or *E4/E3* carriers tend to have higher serum levels of LDL and total cholesterol, compared with their *E2* allele counterparts[85]. However, the *E2* allele confers genetic susceptibility to hypertriglyceridemia. In West Mexico, this allele has been associated with hypertriglyceridemia and early onset of alcoholic cirrhosis[86].

The distribution of the *Apo E* alleles varies both globally and within the admixture Mexican population (Table 1). This genetic variation has been linked with differences in the prevalence and predominance of dyslipidemia reported among the population, as well as their interaction with environmental factors, such as diet. Although the *Apo E2* allele has been associated with European ancestry, *Apo E3* is predominant among the inhabitants of Central Mexico, and the *Apo E4* allele has been associated with African ancestry or Amerindian groups[46]. To date, this allele has one of the highest rates worldwide within the Huicholes population from West Mexico (Table 1). As the *E4* allele reduces the efficiency of cholesterol metabolism, these native carriers could have been protected by their low-fat diet in their natural environment, reinforced by the ABCA1 polymorphism. However, it may become a risk allele when these carriers consume a high-fat urban diet.

Milk and dairy products

Lactase: Lactase is an enzyme expressed in the intestinal microvilli, which hydrolyzes the disaccharide lactose made up by glucose and galactose. In newborns, this enzyme is highly expressed to digest human milk. After weaning, a typical phenomenon known as "lactase non-persistence" takes place and is characterized by the decreased enzyme expression. As a result, the adult lactase activity decline, and lactose cannot be hydrolyzed, presenting poor absorption. However, this result commonly occurs in the presence of *C-13910T* allelic polymorphism at the promoter region of the lactase gene *LCT.* Among the Europeans, the *-13910T* allele has been associated with lactase persistence in adulthood, with a prevalence of this phenotype reaching 90%[87]. In this case, positive selection of this polymorphism, approximately 5000 years ago, could be related to the long history of cattle domestication and consumption of dairy products in this population[88]. In contrast, cattle and dairy products were absent in the Amerindian's pre-Hispanic diet because they were introduced quite recently, after the arrival of the Spaniards[45]. Although

Table 2 Hepatopatogenic diet of the general population of West Mexico (n = 425)

Nutrient	Dietary reference values[1]	mean ± SD
Protein	15%	17.3 ± 4.2
Total fat	< 30%	35.5 ± 8.3
SFAs	< 7%	10.0 ± 3.8
MUFAs	20%	11.5 ± 4.8
PUFAs	10%	4.6 ± 2.5
Cholesterol (mg)	< 200	254.3 ± 144
Total carbohydrates	50%-60%	48.6 ± 8.8
Simple carbohydrates	< 10%	16.7 ± 12.5
Fiber (gr)	30	15.5 ± 9.2
Vitamin A (μg)	1000	805.1 ± 679
Vitamin C (mg)	60	86.4 ± 97.9
Folic acid (μg)	200	148.7 ± 107
Vitamin E (mg)	10	2.8 ± 4.3
Iron (mg)	15	13.1 ± 6.6
Magnesium (mg)	350	219.2 ± 123.5
Sodium (mg)	< 2400	1924.7 ± 947
Selenium (μg)	55-70	35.5 ± 22.1
Zinc (mg)	15	5.7 ± 2.8

Adapted from Ramos-López *et al*[95] 2013. Dietary Reference Values: References[97,98] SFAs: Saturated fatty acids; MUFAs: Monounsaturated fatty acids; PUFAs: Polyunsaturated fatty acids.

the *C-13910* allele distribution has not yet been fully studied among the Latin American population, it is known that the lactose intolerance phenotype occurs in up to 80% of the Mexican adults[89,90]. However, the genetic admixture, following the arrival of the Spaniards and the introduction of livestock and dairy products, has allowed certain part of the population to digest milk in adulthood. The high frequency of the lactase non-persistence phenotype indicates that humans are genetically predisposed to discontinue enzyme production because by nature, breastfeeding is essential only during the first years of life, just as cow's milk is necessary only for her calf. Moreover, given the prevalence of the *ABCA1* and *Apo E* polymorphisms in the Mexican population, dairy foods are high in saturated fat and cholesterol and should be recommended with caution in individuals who have these variants. Thus, regarding the gene-environment balance, people with lactase persistence may benefit from dairy products, yet may be at risk for obesity-related diseases. Moreover, people with lactose intolerance should read the message of their genome: avoid dairy products.

Modern-day diet composition

These few examples show that the current trend of globalized (westernized) diets may not be beneficial for everyone, and increased obesity may be associated with modifications in peoples´ traditional food. Moreover, not all populations worldwide are at the same stage of epidemiological transition, including nutrition transition. In contrast to Europe and the United States, it was not until the second half of the XX century that the westernized lifestyle reached the populations of Latin America[91]. Although this region shares geographic and ethnic/linguistic similarities, it also has considerable genetic and cultural diversity between and within countries[92]. In consequence, the epidemiological transition has been more heterogeneous than in other regions of the world. For instance, countries such as Argentina and Chile exhibit a predominant Caucasian ancestry with consumption of a more western-type diet and have higher rates of excess weight (> 60%), whereas Central America displays a more Amerindian dietary culture, with high intake of grains and vegetables, and prevalence rates range from 30% to 55%[92,93].

Likewise, Mexico is among the most westernized counties of the Americas and is currently in the mists of the epidemic of obesity, with an accumulated prevalence rate of about 70% among the adult population (overweightness and obesity) and 26.2% for children, which constitutes a major risk factor for T2DM, CVD and NAFLD/NASH[93]. The National Nutrition Survey showed that the national overweight prevalence (BMI $\geqslant$ 25) for adults increased significantly from 61.8% in 2000 to 71.3% in 2012[93]. However, the more developed industrial States in Northern Mexico have very similar epidemiological indicators to the ones observed in developed countries, whereas the less developed Central and Southern Mexican States exhibit pre-transitional conditions[94]. These disparities may be associated with the regional genetic and culture differences that have been mentioned before.

Unfortunately, our modern-day diet has shifted away from many of the healthy traditional pre-Hispanic dietary ingredients of the past. The current diet of the Mexican population is characterized by an excessive consumption of industrially sweetened beverages (high-fructose corn syrup), over-fried foods cooked in oil or lard, red meat, and confectionary foods[95,96]. These dietary trends have changed the nutritional composition of the diet by increasing the proportional amount of saturated fatty acids and (SFAs) simple carbohydrates (SC), and have decreased the intake of fiber and important micronutrients such vitamins and minerals. In Table 2, a representative hepatopathogenic diet of West Mexico shows that the population of this region has an excessive amount of macronutrient calories and an imbalanced intake of micronutrients with antioxidant, anti-inflammatory and anti-fibrogenic properties[95,97,98]. It has been documented that the long-term consumption of this unbalanced diet is an important risk factor for the development of obesity and NAFLD/NASH in many countries worldwide[6,7].

REGIONALIZED INTERVENTION STRATEGY

In 2010, the World Health Organization declared that after viral hepatitis and alcoholic liver disease, both NAFLD and NASH would be major global health

Table 3 Features of nutritional treatment for nonalcoholic steatohepatitis recommended by international guidelines

International guide	Body weight reduction	Caloric reduction	Carbohydrates	Fat	Vitamin E	Ref.
WGO	5%-10%	25%	↓ Fructose	↓ SFAs ↑ ω3:ω6 ratio	NI	LaBrecque *et al*[99] 2014
AASLD, ACG, AGA	3%-10%	NE	NE	NE	800 IU/d	Chalasani *et al*[104] 2012
AISF	0.5 kg/wk	NE	↓ Fructose	↓ SFAs	NI	Loria *et al*[105] 2010
ENDO CHINA	3%-10%	500-1000	NE	NE	800 IU/d	Gao *et al*[106] 2013

WGO: World Gastroenterology Organization; AASLD: American Association for the Study of Liver Diseases; ACG: American College of Gastroenterology; AGA: American Gastroenterological Association; AISF: Italian Association for the Study of the Liver; ENDO CHINA: Chinese Society of Endocrinology; SFAs: Saturated Fatty Acids; NE: Not specified; NI: Not indicated.

Table 4 Potential effects of dietary nutrients in the prevention and treatment of obesity and nonalcoholic steatohepatitis

Nutrient	Potential effects	Ref.
Macronutrients		
Complex CHO/DF	Microbiota modulation, protection of gut colonization by pathogenic species, reduction of energy intake	Mann *et al*[107] 2007
MUFAs	Increased fatty acid oxidation and inhibition of lipogenesis	Assy *et al*[108] 2009; Soriguer *et al*[109] 2006
PUFAs	Increased fatty acid oxidation and insulin sensitivity in target tissues, inhibition of lipogenesis and anti-inflammatory	Teran-Garcia *et al*[110] 2007; Stienstra *et al*[111] 2007
Micronutrients		
Vitamins C/E	Antioxidant and anti-fibrogenic	Chang *et al*[112] 2006; Parola *et al*[113] 1992
Choline/folic acid	Hyperhomocysteinemia prevention and lipid transport	Vance[114] 2008
Magnesium	Immunomodulatory, antioxidant and regulation of blood glucose levels	Takemoto *et al*[115] 2013
Vitamin D	Increased insulin sensitivity in target tissues	Takiishi *et al*[116] 2010
Food functional components		
Lycopene	Antioxidant, induction of detoxifying enzymes, anti-inflammatory	Ip *et al*[117] 2013
Polyphenols	Antioxidant, chemopreventive, immunomodulatory, apoptosis and detoxifying enzymes induction, anti-inflammatory and anti-proliferative actions	Scalbert *et al*[118] 2005; Fraga[119] 2007; Pandey *et al*[120] 2009
Probiotics (*Lactobacillus*)	Microbiota modulation, immunomodulatory, production of antibacterial substances and anti-inflammatory effect	Iacono *et al*[121] 2011

CHO: Carbohydrates; DF: Dietary fiber; MUFAs: Monounsaturated fatty acids; PUFAs: Polyunsaturated fatty acids.

problems in the upcoming years[99]. Thus, diagnostic, therapeutic, and management options to address these illnesses should be a top priority at all healthcare levels. Several actions have been implemented to prevent or treat obesity. In general, they often pursue weight loss through lifestyle modifications, such as reducing dietary energy intake, increasing physical activity, and addressing risk behaviors in addition to pharmacological therapy or bariatric surgery[100]. Additionally, a wide variety of commercial diets has been promoted to the general public[101], and government agencies have acted through national campaigns, using "My Plate" from the Dietary Guidelines for Americans 2010[102] in the United States and "*El Plato del Buen Comer*" from the Mexican Official Norm (NOM-043-SSA2-2012)[103]. Regarding the management of NAFLD/NASH, most of the intervention strategies aim to treat liver disease in conjunction with the associated co-morbidities such as obesity, hyperlipidemia, insulin resistance and T2DM[104]. These guidelines have been developed based on systematic reviews and meta-analysis studies that provide general recommendations concerning quantitative and qualitative modifications in carbohydrates, fats (SFAs and Omega 6/Omega-3 ratio) and Vitamin E[99,105,106], as shown in Table 3. However, the pathophysiology of obesity and NASH is highly complicated because more than one nutritional component and metabolic pathway may be affected[95]. Several studies show that multiple nutrients other than the aforementioned may abolish the metabolic risk factors involved in obesity/NASH. These factors include dietary modifications in the macronutrient[107-110]/micronutrient[111-115] composition and functional components[116-120], which have anti-inflammatory, anti-fibrotic, anti-proliferative, antioxidant and immunomodulatory functions, as shown in Table 4. Other micronutrients besides vitamin E, such as vitamins D and C, have also been suggested[112,116]. Lycopene and polyphenols, which may be provided by distinct food sources worldwide, have pleiotropic properties[118,120]. Furthermore, the role of probiotics[121] in the pathogenesis of inflammatory liver disease is an ongoing topic[122], in which prebiotics from foods are an inherent counterpart. Overall, it is obvious that many beneficial nutrients that may aid against obesity/NASH can in fact be part of a natural (non-processed) diet, one that resembles the staple ethnic diets of several traditional societies worldwide, such as the Mediterranean, Japanese/Chinese, Greek, or even Mexico and other Latin American countries. However, it

Table 5 Beneficial nutrient content of the staple diet of Mexico

Scientific name	Common name	Nutrient
Salvia hispanica	Chia	MUFAs, PUFAs, magnesium
Theobroma cacao	Cocoa	MUFAs, magnesium, polyphenols
Zea mays	Maize	Magnesium, choline, vitamin E, MUFAs
Prunus dulcis	Almond	Vitamin E
Phaseolus vulgaris	Bean	Magnesium, choline, PUFAs
Amaranthus caudatus	Amaranth	Choline, magnesium, PUFAs
Psidium guajava	Guava	Vitamin C
Carica papaya	Papaw	Vitamin C
Chenopodium mexicanum	Quelites	Magnesium, vitamin C
Capsicum annuum	Chili	Vitamin C
Solanum lycopersicum	Tomato	Lycopene, vitamin C
Citrullus lanatus	Watermelon	Lycopene
Ictalurus punctatus	Catfish	Vitamin D
Thunnus albacares	Tuna fish	Vitamin D
Cucurbita pepo	Squash seeds	PUFAs
Cucurbita pepo	Squash	Vitamins C and E
Persea americana	Avocado	MUFAs, vitamin E
Lactobacillus spp	*Tejuino*[1], *Pulque*[2], *Tepache*[3]	Probiotics

Adapted from Ledesma-Solano *et al*[126]. MUFAs: Monounsaturated fatty acids; PUFAs: Polyunsaturated fatty acids. [1]Tejuino, fermented maize beverage; [2]Pulque, fermented agave plant beverage; [3]Tepache, fermented fruit beverage, commonly pineapple.

is also true that globally, many populations are losing their food culture[123].

On the other hand, commercial diets and international guidelines are intended for the general population; however, by means of nutritional genomics, the trend for the prevention and treatment of obesity-related liver diseases may now consider the individual's genetic make-up and environmental context. To date, individual genotyping is not feasible in all regions of the globe, so a personalized diet is an idea that still seems distant from application[124]. However, based on what has been discussed in this paper, a country with knowledge of its genetic and food history and of the distribution of the selected nutrient-interacting genes related to ancestral diets, has the advantage of being able to appropriately adjust nutritional recommendations by regions[125]. Thus, an alternative approach could be first to focus on a "region-tailored diet" as at present no effective pharmacological therapy exists for obesity/NASH[99].

In particular, Mexico has been the origin of many endemic and domesticated plants and animals ever since pre-Hispanic times. A regionalized diet is feasible if it is based on local fresh produce, such as seasonal fruits and vegetables, grains and oilseeds that contain low-calorie nutrients and many functional ingredients as depicted in Table 5. In resemblance to the ancestral diet, regional diets could be rich in vitamins, minerals, and folates that are known today to avoid steatosis. The consumption of a high-starch diet rich in complex carbohydrates instead of simple sugars is compensated for by a high number copy of the *AMY1* gene. The *ABCA1, CD36,* and *Apo E* genes speak of a diet low in animal fats, yet adequate in vegetal oils, and avoiding milk and dairy products may be essential. In general, these polymorphisms have a higher prevalence among the native populations; nonetheless, the mestizo population still shares much of its ancestral Amerindian component, indicating a traditional staple diet is still better for healthier nutrition.

Another benefit of the Mexican staple diet is the well-known combination of maize and nixtamalized (alkaline-treated) maize-derived products with beans. These foods not only provide essential amino acids, calcium and niacin[45,126] but also act as natural prebiotics and add extra resistant starch required for a healthy gut metabolism. Moreover, these nutrients were supplemented with the consumption of indigenous fermented-beverages such as *tepache*, *pulque* and *tejuino* that provide complementary probiotics (Table 5). Other ingredients that are not considered in modern-day diets are the medicinal/culinary plants that were often added to the food as species or herbs that are known to be beneficial.

CONCLUSION

Due to the high prevalence of obesity in Mexico and abroad, it appears feasible that any attempt to provide an intervention strategy should be based on the most frequent genetic polymorphisms and food culture of each population. This approach could provide a fitter gene-nutrient interaction that justifies the adoption of a regionalized diet, which is not only socially accepted by the general public, but is also energy-balanced, natural, and nutritious. In the age of globalization, it would only be fair to take advantage of the many Mesoamerican "gifts" that have been given to the world, such as maize, beans, tomatoes, squash, potatoes, vanilla, cocoa, and chili, instead of promoting an apparently well-balanced diet with industrial processed ingredients. Therefore, to combat obesity and its unhealthy consequences, it is crucial to continue analyzing the genetic signature "written" on the human genome. This action may be worth replicating in other populations around the world to achieve sustainable and healthier lifestyles according to the genetic background and food culture of each society.

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ISSN 1007-9327