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Section III
Herbs and Plants for Treating Liver Disease

Chapter 1

Genome-Based Nutrition in Chronic Liver Disease

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1. INTRODUCTION

1.1 Chronic Liver Disease

Liver cirrhosis is a chronic disease that initiates by an inflammatory process with or without accumulation of fat, followed by fibrosis. The degree of fibrosis (F) can be staged F1 (initial), F2 (intermediate), F3 (advanced), and F4 (cirrhosis). Once clinical cirrhosis becomes manifest, the patient may die due to systemic complications of liver cirrhosis or progress to hepatocellular carcinoma.

The main etiological agents that lead to liver cirrhosis are alcoholism, viral hepatitis B and C, and most recently, obesity in subjects that are susceptible to develop nonalcoholic steatohepatitis (NASH). The progression of each disease may last from 25 to 30 years due to differential interactions between genes and key environmental lifestyle factors such as diet, physical activity, and emotional state. Therefore, this time span may be shorter or longer. Furthermore, with the use of noninvasive techniques such as transient elastography or serum markers, liver damage may be detected in early stages (F1–F3) before cirrhosis is present so that an appropriate medical-nutritional therapy can be implemented. The best strategy would be to eliminate the etiological agent to prevent or reverse liver damage. In regard to this point, there has been considerable enthusiasm worldwide for the efficacy of the new antiviral agents for hepatitis B and C,[1] whereas alcoholism has diminished in some developing countries.[2] However, the obesity epidemic is a new threat that compromises the health of liver-diseased patients regardless of the etiology in both wealthy and impoverished countries. Therefore, each nation needs to evaluate the impact of these illnesses to implement nutritional strategies for liver-diseased patients aimed to avoid or reverse the progression of chronic liver diseases and nutrition-related comorbidities.

This obesity epidemic is driven by a global wave of nutritional transition where populations waive their traditional diet and lifestyle. This transition has created an imbalance between the ancestral genes respective to the current lifestyle which has been associated with an increased risk of developing some of the highly prevalent nutrition-related chronic diseases (NRCDs) of today. For example, in the last 50 years, the Mexican population underwent a nutrition transition from a traditional dietary pattern, passing through undernutrition, and currently overnutrition. Excess weight is prevalent in 72.1% of the adult population affecting all socioeconomic statuses but mostly those with low income that comprises more than 50% of the population. Furthermore, the leading causes of mortality are type 2 diabetes, cardiovascular disease, and liver cirrhosis.[3] The leading causes of liver cirrhosis are the excessive consumption of alcohol, followed by hepatitis B and C virus (HCV), and an increasing rate of NASH.[4,5] Furthermore, the main dyslipidemias in Mexico are hypercholesterolemia, hypertriglyceridemia, and hypoalphalipoproteinemia.[6] All three types have been associated with genetic susceptibility combined with a particular dietary pattern described as a hepatopathogenic diet that places individuals at risk for NRCDs as aforementioned.[6,7]

1.2 Hepatopathogenic Diet and Its Variations by Liver Disease Etiology

Among the Mexican population, the characteristics of a hepatopathogenic diet have been defined.[7] This dietary pattern is characterized by an excessive energy intake, an imbalance of macronutrients, as well as a low content of fiber and micronutrients with antioxidant and anti-inflammatory properties such as vitamins A and E, folates, magnesium, selenium, and zinc. Notably, this diet contains a disproportionate amount of simple sugars (>10%), saturated fats (>10%), more than

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200 mg of dietary cholesterol, and an increased ratio of n-6: n-3 polyunsaturated fatty acids (PUFAs) (12:1)[8]. Overall, this unhealthy diet has been associated with the increase in the consumption of industrial food containing high-fructose corn syrup such as sweetened beverages, together with overfried foods cooked in oil or lard, red meat, high-fat dairy products, and confectionery foods. Furthermore, an increase in the number of sedentary activities is common, leading to less calorie expenditure. This dietary pattern has been identified in both lean and excess weight patients, as well as those with chronic liver disease.[7,8] However, the dietary composition of the hepatopathogenic diet may have differential features according to the etiology of liver disease and related lifestyle. For example, it has been documented that patients who are normal weight consume a hepatopathogenic diet containing high amounts of animal fat (saturated fat) obtained from red meat, cold cuts, and processed foods and less amount of fruits, vegetables, legumes, and selenium. However, those with excess weight eat the same diet but consume a lower amount of monounsaturated fats and fish meat. These dietary patterns have been associated with dyslipidemias such as hypercholesterolemia and hypertriglyceridemia, respectively. On the other hand, alcoholic patients present hypertriglyceridemia and consume excess calories through the consumption of carbohydrates (cereals, alcoholic beverages, soft drinks), high cholesterol levels (red meat), and high sodium due to salty snacks.[7] In contrast, patients with HCV manifest metabolic alterations such as hypoalphalipoproteinemia, insulin resistance, and high levels of liver enzymes. These alterations may be related to the metabolic dynamics between circulating lipids and the viral particle. However, despite the fact that they tend to consume a healthier diet compared with the other groups of patients, most of them are overweight and obese, suggesting the influence of the hepatopathogenic diet.[7] In conclusion, an adequate dietary intervention should be oriented to reverse the hepatopathogenic effect of this diet based on the identification of food group responsible for the excess calories, nutrient imbalance, and metabolic dysfunction in each etiology of liver disease.

2. GENOME-BASED NUTRITION: A REGIONALIZED AND PERSONALIZED DIET

Genomic medicine provides a new approach to how health professionals prevent, manage, and treat many types of diseases. Regardless that they may be infectious or noncommunicable, the onset and progression will depend on the presence of genetic and environmental risk factors.[9] In the field of nutritional genomics, genome-based nutrition refers to a strategy that considers the population's or individual's genetic background and lifestyle to set tailored nutritional recommendations or interventions. Most modern-day NRCDs may be considered as an imbalance between several ancestral polymorphic genes generated by gene-culture coevolutionary processes and the current-day lifestyle.[10] Therefore, restoring this balance should be the main target of a nutritional genomic therapy in which the correct diet that should be recommended to healthy individuals would take into account ethnicity, genetics, and cultural, social, and environmental factors of the population they belong to.[11] The morbidity and mortality due to NRCDs have been tackled in some countries by promoting the consumption of traditional diets or integrating regional foods, as in the case of the Mediterranean-type diet.[12] However, each region provides its biodiversity with differences in genotype frequencies, food products, and food culture.

As an example, genome-based nutrition strategies in Mexico would include the knowledge of the Mexican genome and the food cultural history of the population. First, the Mexican population is an admixture of the ancestral Amerindian population with Caucasian and African lineages.[11] However, this admixture is heterogeneous throughout the country.[13] Therefore, it is expected that the proportion of the ancestral Amerindian genes vary from 50% to 100% based on the geographic location and demographic history of the population. Second, the Mesoamerican diet is the basis of the Mexican food culture.[14] However, this traditional diet is widely diverse in regional food ingredients as the result of the miscegenation between the Old and New World cultural food patterns. However, these regional diets have evolved toward the westernized and hepatopathogenic diet that currently has a negative impact on the population's health. Given these antecedents, studies have been carried out to evaluate the prevalence profile of some diet-related adaptive gene polymorphisms to determine the dietary features to which the Mexican population is genetically adapted. These studies have shown that diet-related gene polymorphisms have a heterogeneous distribution in which the ethnic groups (Amerindians) revealed the highest frequencies of adaptive alleles such as *MTHFR* 677T, *ABCA1* 230C, and *APOE* ε4 followed by mestizos, while the mean of *AMY1* diploid copy number was 6.82 ± 3.3 copies.[15] Nonetheless, the frequency of the European-related *LCT*-13910T adaptive allele was highest in mestizos with high European ancestry but extremely low in Amerindians.[16] The abovementioned diet-related genes are involved in folate (*MTHFR*) and lipid (*ABCA1* and *APOE*) metabolism, as well as in dairy (*LCT*) and starch (*AMY1*) digestion. Being carriers of adaptive alleles may require nutritional specifications related to traditional dietary practices to avoid the risk of disease to which they have currently been associated. For example, the highly prevalent *MTHFR* 677T may demand an adequate folate intake or even higher than the Recommended Daily Allowances for the general population. The high frequency of *ABCA1* 230C and *APOE* ε4 suggests a genetic adaptation to low-saturated fat/cholesterol diet, so the excess in the consumption of these nutrients should be discouraged. Furthermore, a mean *AMY1* gene copy number of ≥6 copies is consistent with agricultural societies capable of digesting high-starch foods, and the low

prevalence of the European *LCT*-13910T allele indicates that this population is not genetically adapted to digest dairy in adulthood. Therefore, the consumption of milk and dairy products as essentials of the diet should not be recommended. Furthermore, the association of the risk alleles of some taste receptor genes such as *TAS1R2*, *TAS2R38*, and *CD36* with dyslipidemia and liver damage should not be neglected.[17–20]

Thus, to modify the current hepatopathogenic dietary pattern, genome-based nutritional advice should be tailored in a regionalized or individualized manner according to the genetic background, regional foods, and traditional food culture of each population. Once the correct diet has been established, specific modifications can be made as required for each liver disease, for example, a correct diet plus antioxidant foods for NASH or a correct diet plus anti-HCV nutrients for patients with chronic HCV infection. This action may be worth replicating in other populations around the world to achieve sustainable and healthier lifestyles.

3. GENES, MICROBIOTA, AND REGIONALIZED DIET

Beneficial bacteria from the intestine confer numerous health benefits to the host, including metabolism regulation, energy homeostasis, intestinal motility, immune system control, and host behavior regulation.[21] However, gut microbiota alterations facilitate the progression of chronic diseases such as obesity, cardiovascular diseases, type 2 diabetes, nonalcoholic fatty liver disease (NAFLD), as well as altered emotions and eating behaviors.[22,23] Factors such as the type of birth, diet, alcohol consumption, viral infections, stress, age, body weight, exercise, use of antibiotics, genetics, and geography modify gut microbiota composition.[24] The study of gene polymorphisms and environment interactions with gut bacteria is the main focus of research to understand the development of chronic diseases and negative emotions.[25]

The central nervous system maintains bidirectional communication with the intestine. Moreover, in the presence of energy balance/brain reward system alterations, negative emotions and stress promote the release of cortisol. Cortisol results in dysbiosis, allowing pathogens and toxins to permeate the gut barrier and activate inflammation.[26] Cytokines such as TNFα and IL-1β facilitate abnormalities in lipid metabolism, signal insulin, promote apoptosis, impair lipid oxidation, and promote fibrogenesis.[27] In an excess energy intake from a westernized type of diet, the input and type of short-chain fatty acids (SCFAs) are associated with a higher energy source, lipid accumulation, and liver damage.[28,29] Concretely, acetate and propionate are involved in hepatic lipogenesis and gluconeogenesis.[28] Probiotics, prebiotics, functional nutrients, and different dietary strategies are used to restore the balance in gut microbiota community. Emerging evidence shows that probiotics improve liver metabolism. One way of doing so is by preventing intestinal fat absorption, reducing fasting, and postprandial nonesterified fatty acids levels as showed when *Lactobacillus gasseri SBT2055* in fermented milk was administered.[30] Other probiotics contribute to SCFA production such as MIYAIRI 588 strain of *C. butyricum* which produces butyrate and in this way, prevents hepatic lipid accumulation, improves gut barrier permeability, and suppresses hepatic oxidative stress.[31] Regarding prebiotics, dietary interventions provide prebiotics such as inulin and galacto-oligosaccharides, guar gum, hemicellulose, glutamine, pectin, and other oligosaccharides.[32] These prebiotics produce SCFAs that contribute to increases in beneficial microorganisms such as *Bifidobacteria* and *Lactobacilli*, which are involved in protection against obesity as they inhibit the adhesion of pathogenic microorganisms to intestinal mucosa that could alter permeability.[33] Also, intestinal fermentation of fructans increases incretin production such as GLP-1 and GLP2 secreted by intestinal lumen cells, which regulate insulin secretion by pancreatic B cells, promoting satiety.[34] Dietary strategies based on a more regionalized concept such as the Mediterranean diet have proved to restore gut microbiota in obese patients.[35] This diet improves gastrointestinal symptoms and increases adherence to dietary treatment.[36] These promising results relate to the antioxidant, anti-inflammatory, and prebiotic capacity of Mediterranean foods such as tea, fermented milk products, vegetables, wheat bread, rice, chocolate, coffee, and many others.[37] However, efficient response to foods is influenced by genetic adaptations to the environment.[11,15] Recently, in Mexico, regional prebiotic foods (maize, beans, tomato, prickly pear, and chia and pumpkin seeds) based on the components of the Mesoamerican diet showed increments of beneficial bacteria that promote reductions in metabolic parameters, body composition, adipocyte size; decrease oxidative stress markers; and improve cognitive parameters in an experimental model.[38] Both of these regional dietary strategies prevent chronic disease development and increase the level of treatment compliance by restoring the gut bacteria community, meaning that emotions and modulation of behavior by the gut microbiota need to be considered in the management of obesity and gastrointestinal and chronic liver diseases.[25]

4. NUTRITIONAL INTERVENTION IN CHRONIC LIVER DISEASE

Management of chronic liver disease requires that patients are provided with a comprehensive medical and nutritional intervention. In the case of NAFLD/NASH, reversing the metabolic abnormalities induced by obesity is a primary goal, whereas halting the consumption of alcohol in patients with alcoholic liver disease (ALD) or fighting HCV with antivirals