Chapter 4
Liver and Nutrition

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Situated beneath the diaphragm in the upper right part of the abdomen, the liver is the largest organ in the body (weighing 1–1.5 kg in adults). All of the blood that leaves the stomach and intestines must pass through the liver before reaching the rest of the body. The liver processes nutrients and drugs absorbed from the digestive tract into forms that are easier for the rest of the body to use. In essence, the liver is the body's refinery. Furthermore, this organ plays a principal role in removing toxins from the blood whether they were ingested or internally produced. The liver converts them to substances that can be easily eliminated from the body. And, in addition, it modifies many drugs governing their activity in the body. The liver also makes bile, a green-yellow fluid, which contains detergent-like substances essential for digestion. Bile is stored in the gall bladder, which contracts after eating and discharges bile into the intestine.

Nutrition and the liver are interrelated in many ways. Some ways are well understood; others are not. The liver plays a key role in converting food into the chemicals essential for life, and it serves several important metabolic tasks in handling nutrients (Table 4.1). Carbohydrates (sugars), absorbed through the lining of the intestine, are transported through blood vessels to the liver and then converted into glycogen and stored. The liver breaks down this stored glycogen between meals releasing sugar into the blood for quick energy to prevent low blood sugar levels (hypoglycemia). This enables us to keep an even level of energy throughout the day. Without this balance, we would need to eat constantly to keep up our energy.

The liver is vital in maintaining the body's protein and nitrogen metabolism. Proteins in foods can be broken down into amino acids in the intestine and delivered to the liver for use in making body proteins. Excess amino acids are either released

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Table 4.1 Liver metabolic functions according to the type of nutrient/compounds

Liver metabolic functions			
Carbohydrates	Lipids	Proteins	Others
Converts carbohydrates to glucose	Builds and breaks down triglycerides, phospholipids, and cholesterol as needed	Makes nonessential amino acids that are in short supply	Detoxifies alcohol, other drugs, wastes, and poisons
Makes and stores glycogen	Breaks down fatty acids for energy when needed	Removes from circulation amino acids that are in excess and converts them to other amino acids	Helps dismantle old red blood cells and captures iron for recycling
Breaks down glycogen and releases glucose	Packages extra lipids and transports them to other body organs	Removes ammonia from the blood and converts it to urea to be sent to the kidneys for excretion	Stores some vitamins and minerals
Breaks down glucose for energy when needed	Makes bile to send to the gallbladder for use in fat digestion	Makes other nitrogen-containing compounds the body needs (e.g. DNA & RNA)	Forms lymph
Makes glucose from amino acids and glycerol when needed	When needed, makes ketone bodies when necessary	Makes plasma proteins such as clotting factors	

by the liver and sent to the muscles for use or are converted to urea for excretion in the urine. Certain proteins are converted into ammonia, a toxic metabolic product, by bacteria in the intestine or during the breakdown of body protein. The ammonia must be detoxified by the liver and made into urea, which is then excreted by the kidneys. Through the production of bile, the liver makes it possible for dietary fat to be absorbed. In addition, vitamins A, D, E, and K, which are fat soluble, are dependent on bile from the liver for absorption.

Many chronic liver diseases are associated with malnutrition. For instance, Metabolic Associated Fatty Liver Disease (MAFLD), a condition characterized by a build-up of fat in the liver that affects over one billion people, is tightly associated with obesity, type 2 diabetes (T2D), and Metabolic syndrome (MetS). MAFLD entails a broad spectrum of conditions, spanning from simple and uncomplicated steatosis to nonalcoholic steatohepatitis (NASH), which is characterized by hepatocyte ballooning, lobular inflammation, and fibrosis that could worsen into cirrhosis and hepatocellular carcinoma (HCC) [1, 2]. MAFLD pathogenesis is closely entangled with increased adiposity, insulin resistance (IR), and dyslipidemia [3]. Indeed, dietary habits such as excessive caloric intake, high fructose consumption, and poor physical activity represent paramount risk factors for this condition [4]. In the last decades, the prevalence of metabolic disorders (e.g., MAFLD, obesity, and T2D) has exponentially increased in Western countries. This escalation is strictly correlated

with changes in dietary habits. Indeed, the Western diet is evolutionally modified, replacing fruits, vegetables, proteins, and omega-3 fatty acids with saturated and trans-fat, omega-6 fatty acids, carbohydrates, and high-energy nutrients [5]. It has been demonstrated that nutritional and lifestyle interventions exert beneficial effects on MAFLD outcomes and its comorbidities.

The human gastrointestinal lumen is the largest reservoir of microorganisms in the body, representing the physiological habitat for more than 100 trillion microorganisms (bacteria, archaea, fungi, yeast, and viruses) [6]. Among them, 85% of total bacteria are commensal microbes that live in synergy with the host, providing biological and metabolic functions. All abnormalities in intestinal flora taxonomic composition and/or function are usually referred to as 'dysbiosis,' a condition that has been largely explored in rodents and MAFLD patients [7, 8]. The dietary habits along with the caloric intake may strikingly contribute to the inter-individual variability of the intestinal bacterial strains. Indeed, a diet composition unbalanced in animal fat and sugars may more strongly increase the personal susceptibility to pathogenic bacteria over-growth, exerting a detrimental effect on the immunological tolerance of mucosal cells, as shown in a large number of preclinical [9, 10] and clinical studies [11, 12] Western diet and High Fat Diet (HFD) have been related to the increased amount of pro-inflammatory bacterial species, altering gut barrier integrity, intestinal pH and lipopolysaccharide (LPS) transition into the blood flow (endotoxemia) [13]. Indeed, the intestinal barrier is constituted by tight and adherent junctions and desmosomes, which hold together the epithelial cells and regulate the bidirectional flux between the gut and the liver. Specifically, the intestinal barrier protects the host from pathogen invasions and impedes microbial systemic translocation [7]. Dietary modifications can rapidly normalize intestinal microbiota, thus representing a simple and effective approach to restoring eubiosis. Indeed, the diet is enabled to profoundly reshape the microbiota composition within a few hours. People consuming a Western diet and subjects with high-fiber dietary habits display a tremendous difference in microflora taxonomic composition, as shown in an elegant study in which American volunteers were randomized to receive an animal-based diet (meats, eggs, and cheese) or a plant-based diet (cereals, legumes, fruits and vegetables). Natural extracts, such as polyphenols provided by coffee, green tea, and chocolate, have been demonstrated to induce beneficial effects by directly interacting with gut microbial communities. In C57Bl/6 mice fed HFD, grape polyphenols administration improved insulin sensitivity, attenuated inflammation, and ameliorated intestinal barrier integrity. Overall, diets enriched in phenols have been associated with improved MetS features and immune tolerance, and with the restoration of intestinal barrier function, by promoting eubiosis.

Nutritional genomics studies the impact of nutrients on gene expression, genome evolution and selection, genome mutation rate, and genome reprogramming [14]. It entails even the detrimental effect exerted by specific macro and micronutrients on DNA metabolism, addressing mainly their role in DNA synthesis, degradation, repair, and alteration. In turn, genomic evolution and selection may contribute to the genetic variations observed within genetically different ethnicities. An important aspect *of nutrigenomics* is the effectiveness of nutrients (especially micronutrients) on DNA metabolism, even though it is not deeply investigated. Some evidence supports

the notion that several micronutrients are required to maintain DNA homeostasis, as they are cofactors of a variety of enzymes involved in DNA synthesis and repair [15]. Thus, nutritional deficiency of these essential micronutrients could induce a strong DNA modification comparable to that observed after DNA exposure to mutagenic substances or radiations [16]. Another area of interest of nutrigenomics is represented by *nutrigenetics*. The latter entails the study of the effect of a genotype (e.g., the presence of SNPs or other genetic variations) towards specific dietary patterns. Indeed, each subject could respond differently to nutritive substances, and genetic variations within different human populations are a consequence of the adaptive evolution to specific dietary habits. Common SNPs in DNA sequence constitute the primary example of genetic variation. They arise from a process of DNA mutation and subsequent selection in the populations. Nutritional environment intervenes in this evolutionary process, precipitating the expansion of DNA mutations within the subjects.

Epigenetics is a hereditable but reversible phenomenon that affects chromatin ultrastructure and transcription without modifying DNA sequence in response to environmental cues including DNA methylation, histone modifications, and miRNAs targeting mRNA [4, 17]. The emerging knowledge of '*nutriepigenomics*,' referred to as the interaction between nutrients and genome through epigenetic mechanisms, is increasingly grabbing attention in the field of human complex diseases such as MetS, neurological disorders, and cancer [18]. The hypothesis of the Developmental Origins of Adult Health and Disease underlined that exposure in utero to environmental stressors, such as diet, had intergenerational effects, compromising adult phenotype [19]. Hence, food intake could affect epigenome remodeling throughout life and, interestingly, several dietary habits could be critical during gestational and post-natal periods, leading to stable epigenetic changes, which, in turn, could impact metabolic disease susceptibility [4, 18]. Likewise, it has been reported in both animals and humans that risk factors, such as maternal obesity, could predispose descendants to metabolic disorders due to an imprinted metabolic signature induced on microbiota during pregnancy [18].

If on the one hand junk food and a sedentary lifestyle cause metabolic dysfunction, on the other hand, the study of nutrigenetics/epigenetics enables us to identify either different genetic polymorphisms, which may modulate the effectiveness of nutrients, and epigenetic markers that may be potential therapeutic targets of specific dietary interventions. Bioactive substances, such as polyphenols, flavonoids, fish-derived oils, and, in general, compounds enriched in the MedDiet, predominantly consisting of fruits and vegetables, have shown systemic benefits as preventive and curative molecules for metabolic diseases, cardiovascular risk, and cancer [20, 21]. Apple polyphenols and red wine extract as resveratrol and derivates have been shown to epigenetically prevent diet-induced obesity and ameliorate liver injury and cardiac dysfunction [22–25]. For instance, curcumin acts as a free radical scavenger and hampers lipid peroxidation and oxidative DNA damage. In a randomized double-blind placebo-controlled trial, the short-term curcumin administration in MAFLD patients improved hepatic fat content and metabolic profile (trial registration IRCT20100524004010N24) [26]. In addition, it has been demonstrated that

curcumin exerts hepatoprotective effects on fibrogenic processes [25]. Green tea, rich in polyphenols and catechins, is a natural hypolipidemic, antioxidant, and thermogenic agent whose beneficial effects on hepatic steatosis and liver damage have been widely studied in both genetically and dietary-induced experimental models of MAFLD/NASH [27–31].

The Western human diet has evolutionally changed, and nowadays, it is markedly enriched in saturated and trans-fat, omega-6 fatty acids, carbohydrates, and high-energy nutrients against fruits, vegetables, proteins, and omega-3 fatty acids [5]. Nutritional genomics addresses the gene-environment interactions and the detrimental effect of the changes in our dietary landscape. It may represent a promising tool to revolutionize both clinical and public health nutrition practice and may favor the establishment of genome-informed nutrient and food-based dietary guidelines for disease prevention and a healthy lifestyle, individualized medical nutrition therapy for MAFLD management, and better-targeted health nutrition interventions, including micronutrient supplementation, maximizing the benefits and in turn minimizing the adverse outcomes within genetically diverse human populations [14]. In this context, the study of nutriepigenetics is becoming increasingly attractive, as it would allow the identification of novel appealing bioactive compounds, which may contribute to modulate the hepatic epigenetic signature from the maternal and lactation period onward.

To date, no therapeutic strategy is approved for the treatment of MAFLD, and lifestyle modifications, physical exercise, and weight loss remain the cornerstone of approaches to patients with MAFLD. Indeed, personalized nutritional recommendations for MAFLD patients remain largely unexplored and a deep understanding of the mechanisms behind gene-environment interactions should be a priority for future research. Considering nutrigenomics as an option will guarantee us the clef to compose the harmonic combination of nutrients suitable for our genome, orchestrating the perfect symphony of health. A better knowledge of diet-genome interactions will allow applying new approaches to the prevention and treatment of chronic disorders by using precision nutrition, which might be included in the personalized medicine therapy. However, the amount of studies is scarce and nutrigenomic research remains largely inconclusive. Therefore, there is an urgent need to increase the number of experimental data to unravel these mechanisms and to discover novel appealing candidate biomarkers for diagnosis as well as to introduce nutraceutical products as a preventive or therapeutic strategy [5].

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