Review Article

Association Between Precision Nutrition and Microbiome for Targeting Cardiometabolic Diseases, Inflammation and Bone Metabolism

Giuseppe Merra[1*], Annunziata Capacci[2], Giuseppe Cenname[3], Ernesto Esposito[4], Maria Dri[5], Laura Di Renzo[1], Marco Marchetti[1]

[1]Section of Clinical Nutrition and Nutrigenomic, Department of Biomedicine and Prevention, University of Rome Tor Vergata, 00133 Rome, Italy

[2]Department of Medical and Surgical Sciences, Agostino Gemelli General Hospital Foundation-IRCCS, Rome, Italy

[3]Comando Generale Arma Carabinieri, Direzione di Sanità, 00197 Rome, Italy

[4]Department of Human Policies [General Directorate] of Basilicata Region, 85100 Potenza, Italy

[5]Department of Surgical Sciences, School of Applied Medical-Surgical Sciences, University of Rome Tor Vergata, 00133 Rome, Italy

[*]**Corresponding Author:** Giuseppe Merra, Section of Clinical Nutrition and Nutrigenomic, Department of Biomedicine and Prevention, University of Rome Tor Vergata, 00133 Rome, Italy

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Abstract

Since ancient times, it is believed that food has a profound influence on the state of health / disease of an individual. To translate genetic information into evidence-based nutritional recommendations it is appropriate to make a critical analysis of the interactions of polymorphisms with nutrition and health. The most recent discoveries on the human genome provide us the tools and the basis for understanding the molecular mechanisms by which individual genes, or combinations thereof, respond to changes in diet and lifestyle. Nutrigenetics concerns the identification of genetic variations in humans that

cause differences in the phenotypic response to molecules introduced with the diet, with the aim of assessing the risks and benefits for the individual of certain components of the diet. In the medical field, the new knowledge on the Human Genome has allowed the consolidation of a new molecular dimension of medicine, in particular of a sector defined as "Predictive Medicine", that is a medicine, which, based on the information obtainable from the genetic constitution of an individual, can anticipate an estimate of the latter's risk of developing a given disease during the course of life. In summary, development of personalized nutrition based on the features of the microbiome is currently being attempted.

Key words: Microbiome; Inflammation; Nutrition

1. Introduction

It is now widely believed that the same nutritional approach in different individuals produces different effects. The advent of omics technologies [1] would confirm how the genetic background plays a key role in the individual response to diet, lifestyle and in the formulation of individual nutritional needs. Moreover, since ancient times, it is believed that food has a profound influence on the state of health / disease of an individual (Hippocrates of Kos, 460 BC, "Let food be your medicine and that medicine be your food"). Similarly, today we could say: "man is the set of gene-nutrient interactions"!. To translate genetic information into evidence-based nutritional recommendations it is appropriate to make a critical analysis of the interactions of polymorphisms (the most frequent form of variation in the genome, greater than 1% in the population) with nutrition and health, which also includes the effect, or the identification of appreciable changes such as to determine significant responses.

2. Nutrigenetics

The most recent discoveries on the human genome provide us the tools and the basis for understanding the molecular mechanisms by which individual genes, or combi-nations thereof, respond to changes in diet and lifestyle (exposure to cigarette smoke, alcohol consumption, etc.), making an individual particularly sensitive to contracting a certain type of pathology and shedding light on the mechanisms by which diet, by in-fluencing gene expression, can exert a protective effect [2]. Ultimately, the potential offered by this new approach introduces us to a new era of nutrition science, nutrigenetics. Nutrigenetics concerns the identification of genetic variations in humans that cause dif-ferences in the phenotypic response to molecules introduced with the diet, with the aim of assessing the risks and benefits for the individual of certain components of the diet. In practical terms, with nutrigenetics it is possible to develop personalized nutrition to the genetic constitution of the individual, taking into account the variability of the genes in-volved in the metabolism of the nutrient and its target. Nutrigenetics can make use of powerful tools capable of providing specific, individual and early information, compared to traditional diagnostic systems, on the preventive role played by nutrients. Bio-molecular techniques have been developed to characterize genes and elucidate the interactions between these and nutrients. The conceptual basis of this new branch can be summarized in the following points:

• the compounds introduced with the diet can exert direct or indirect effects on the human genome, altering the expression and / or structure of genes;

• the diet can represent a risk factor or a prevention tool for degenerative diseases;

• the degree to which diet can influence the health/disease balance depends on the genetic makeup of each individual;

• a nutritional intervention based on knowledge of the individual's genotype and nutri-tional status can be used to prevent or treat pathologies.

2.1 Predictive medicine

The Human Genome Project has delivered to the international scientific community a genetic sequence of three billion base pairs shared 99.9% by all individuals. The dif-ferences between individuals are mostly made up of nucleotide polymorphisms, or changes of a single base in DNA. In the medical field, the new knowledge on the Human Genome has allowed the con-solidation of a new molecular dimension of medicine, in particular of a sector defined as "Predictive Medicine", that is a medicine, which, based on the information obtainable from the genetic constitution of an individual, can anticipate an estimate of the latter's risk of developing a given disease during the course of life [3]. The interest in the genetic component of susceptibility to complex diseases is becoming increasingly important in modern medicine, as the role of some relatively common genetic polymorphisms is being highlighted, but which when associated with each other and combined with specific environmental components, they can significantly increase the risk of developing diseases that are widespread in industrial society

2.3 Personalized nutrition

With nutrigenetics, the concept of "personalized" medicine is extended to the area of nutrition. Individual genetic variability, determining how nutrients are assimilated, me-tabolized, accumulated and ultimately excreted, is the basis of each individual's peculi-arity in responding to the molecules introduced into the body and, in general, to dietary and lifestyle styles. Undoubtedly, however, the most fascinating of the opportunities that open up in the field of nutrigenetics is the development, starting from individual genetic differences, of a "personalized nutrition", in order to obtain an effective "healthy" dietary therapy capable of preventing or delaying the 'onset of food-related pathologies, for single individuals or for particular subgroups [4,5].

2.2 Gene-diet interaction

The concept that the knowledge on the nutritional requirements, the nutritional status and the genotype of an individual or a subgroup of the population can be used for the prevention and treatment of certain diseases is easy and immediate to understand regarding situations such as deficiencies. nutritional, but certainly less obvious for a group of about 50 human genetic diseases caused by the presence of variants in genes that code for enzymes involved in specific metabolic pathways. Each of our genes has about 10 differences in its "code" compared to the "standard gene", these deviations are called "polymorphisms" (SNPs = single gene polymorphisms) and the resulting variants "alleles". It is obvious that, given the relative high frequency with which these mutations occur in the genome, not all polymorphisms cause serious health implications, but most of them exhibit only a slight effect on the functionality of the protein for which they en-code. The resulting individual differences may explain why not all of us react identically to various stresses and nutrigenomics precisely describes the changes in gene expression following a specific nutritional intervention [6]. The molecules we introduce with the

diet can modulate specific aspects of cellular physiology, acting as ligands for transcription factor receptors, altering the concentrations of substrates and metabolites and, through interactions at the level of nucleic acids, influencing specific signal translation pathways.

2.4 The Metabolism of Lipids

Lipids are the most studied determinants of cardiovascular disease and under-standing the molecular mechanisms underlying lipid metabolism disorders is of great importance for the prevention of cardiovascular disease. The genes involved in the regulation of lipid metabolism identified so far are very nu-merous and the list is not yet complete. It is also known that the homeostasis of lipid metabolism is also regulated by various non-genetic environmental factors such as ciga-rette smoking, alcohol consumption, diet composition and physical activity. Although at the current state of knowledge it is not possible to accurately establish the contribution of genetic factors and environmental factors in the etiology of dyslipidemia, however, cases in which a dyslipidemia occurs due to a genetic alteration in the absence of an environmental context are very rare. predisposing, and even in these cases the en-vironmental factors are however able to modulate the severity of the metabolic disorder and to influence the age in which it occurs. From a public health point of view, nutrition is the most important environmental factor that interacts with our genes in modulating the onset of lipid metabolism disorders. It is known that the plasma lipid concentration is greatly influenced by the saturated fat content of the diet and that at the population level the average cholesterol concentrations are higher in those countries that consume diets rich in saturated fat and lower in the countries with diets. low in fat and rich in vegetables and fiber. However, at the individual level, the variation in plasma lipids in response to dietary changes is variable, some subjects respond very well, while others are relatively insensitive. In some cases, high cholesterol levels have been observed in correlation to specific gene mutations, and people carrying these mutations are at high risk for cardiovascular disease.

- Apolipoprotein A1 (APOA1): polymorphism -75 G>A

Apolipoprotein A1 (APOA1) constitutes the major protein component of high-density lipoproteins (HDL, the so-called good cholesterol). Since APOA1 plays an important role in reverse cholesterol transport, low serum APOA1 / HDL levels represent a well-known risk factor for coronary artery disease (CAD). A frequent polymorphism of the APOA1 gene localized in the promoter region, -75G> A, modulates the expression of apolipo-protein A1. Important interactions between this polymorphism, dietary habits and HDL levels are well known. Carriers of the allelic variant of the -75G> A polymorphism may increase their serum HDL level in response to increased dietary intake of unsaturated fatty acids [7].

- Apolipoprotein B (Apo B): R3500Q mutation

Apolipoproteins are proteins belonging to the VLDL and LDL complexes (Very Low Density Lipoproteins and Low Density Lipoproteins) and are responsible for the solubility of lipids in the blood and their reabsorption in cells. In particular, apolipoprotein B-100 (Apo B-100) is necessary for the solubility and reabsorption of cholesterol. The Apo B-100-cholesterol complex is recognized by the LDL membrane receptors and then re-absorbed into the cells. The gene encoding Apo B-100 is subject to

polymorphisms of which, the most frequent (R3500Q), causes a decrease in the affinity of the Apo B-100- "membrane LDL receptor" bond. The mutated Apo B-100 remains free in the blood, causing hypercholesterolemia and an increased risk of obstructive plaque formation. Furthermore, the mutation of this protein is an important risk factor for the development of early atherosclerosis and coronary artery disease (CAD). It has been shown that 3.5% of cases of hypercholesterolemia have a mutation on the Apo B-100 gene as the primary cause. This type of mutation is also known clinically as Familial Defective apolipoprotein B-100 (FDB). Studies on patients with FDB have shown that their cholesterol level is on average 8 mmol / l, while the normal value is less than 5.2 mmol / l. The mutation of this gene, which is located on chromosome 2, causes the protein to replace the amino acid Arginine with a Glutamine in position 3500 (R3500Q); this exchange between amino ac-ids results in a change in the conformation of the tertiary structure of Apo B-100, in the recognition area for the LDL receptor. The decrease in affinity between Apo B-100 and LDL receptor can be greater than 20% in homozygous patients. The prevalence of this mutation in the Caucasian population ranges from 1: 700 to 1: 500 [8].

- Apolipoprotein C3 (APOC3): polymorphisms C3175G and T3206G

Apolypoprotein C3 (APOC3) plays an important role in lipid metabolism, inhibiting the metabolism of triacyl-glycerol by the enzyme lipoprotein-lipase, with a consequent in-crease in the level of triglycerides (hypertriglyceridemia). The C3175G and T3206G polymorphisms of the APOC3 gene are associated with a four times higher risk of hy-pertriglyceridemia and an elevated risk of heart attacks, atherosclerosis and cardiovas-cular diseases [9,10].

- Apolipoprotein E (APO E): genotyping of alleles E2, E3, E4

The APOE gene is located on chromosome 19 and encodes apolipoprotein E (APOE), a plasma protein involved in the transport of cholesterol, which binds to the amyloid pro-tein. There are three isoforms (different structural conformations of the same protein) of ApoE: Apoε2, Apoε3 and Apoε4, which modulate the impact of the diet on the concen-tration of plasma lipids. These isoforms are the products of three different allelic forms (ε2, ε3, ε4), determined by the change of the amino acid in two different positions (variants Cys112Arg and Arg158Cys). Apolipoproteins play a fundamental role in the catabolism of lipoproteins rich in triglycerides and cholesterol. APOE is synthesized mainly in the liver and has the function of a lipid transporter. It has long been known that high cholesterol levels are one of the major risk factors for cardiovascular disease. In particular, not only the total cholesterol level but also the relative levels of HDL, LDL and tri-glycerides are of considerable importance in the pathogenesis of vascular diseases. APOE was one of the first genetic markers to be studied as a risk factor for myocardial infarction. Studies carried out on a large population of patients with myocardial infarction and its control group confirmed data already present in the literature where the ε4 allele of APOE (APOE4) was considered a genetic risk factor for cardiovascular disease. In fact, carriers of allele 4 have higher levels of total and LDL cholesterol, in the presence of a diet rich in cholesterol, and therefore have a greater risk of developing cardiovascular diseases. However, these subjects are also those who respond best when subjected to low-fat diets, while carriers of the

ApoE2 and 3 variants have variable responses [11-14].

- Cholesterol ester transfer protein (CETP): polymorphisms G279A and G1533A

CETP is involved in lipid metabolism, mediating the exchange of lipids between lipo-proteins by transferring cholesterol esters from HDL to triglyceride-rich lipoproteins, resulting in a reduction in HDL levels. The polymorphism of intron 1 of the CETP G279A gene increases CETP concentrations and reduces HDL levels in favor of LDL and VLDL. Another polymorphism, G1533A, located in exon 15 of the CETP gene, which determines the amino acid variation Arg-> Gln at the level of codon 451, is also associated with an increased plasma activity of CETP. Reduced HDL levels are associated with an increased risk of cardiovascular disease [15,16].

- GAP JUNCTION PROTEIN ALPHA 4 (CONNECTION 37): Variant Pro319Ser

Connesina 37 (CX37) is an important molecular factor involved in the development of arteriosclerotic vessels. CX37 is expressed in endothelial cells and is encoded by the GJA4 gene. An amino acid variant at the level of codon 319 (Pro319Ser) of this gene constitutes a prognostic marker for the development of arteriosclerotic plaques and a genetic risk marker for arteriosclerosis [15,16].

- Hydroxy-methyl-glutaryl-coenzyme A reductase (HMGCR): polymorphism -911 C-A

Hydroxy-methyl-glutaryl-coenzyme A reductase (HMGCR) is a gene that codes for the protein of the same name. This is a key enzyme for the synthesis of cholesterol. It has al-ready been mentioned previously that high cholesterol levels are a risk factor for cardi-ovascular diseases, since they predispose to the formation of atherosclerotic lesions. It is interesting to note that given its strategic position in the biosynthetic chain that leads to the synthesis of cholesterol, HMGCR is also the pharmacological target of statins, a family of drugs that act by lowering cholesterol levels. This effect is obtained by inhibiting the enzymatic action carried out by the HMGCR. On the basis of these observations, a polymorphism has been studied in the promoter region of the HMGCR gene at position -911 which consists in the replacement of a C (cytosine) with an A (adenine). This poly-morphism has been studied in a large cohort of patients with myocardial infarction and its control group. The polymorphism was found to be associated with an increased risk of developing myocardial infarction. In particular, the presence of A in the HMGCR poly-morphism was associated with a heart attack at a young age [17,18].

- Lipoprotein lipase (LPL): C1595G polymorphism

Lipoprotein lipase (LPL) is an enzyme involved in the metabolism of triglycerides into circulating lipoproteins. This enzyme is synthesized by the cells of adipose and muscle tissue and after being secreted it is transported to the endothelium of the capillaries, where it interacts with lipoproteins rich in triglycerides. LPL improves the absorption of lipoproteins by the liver and blood vessel walls. The C1595G polymorphism appears to have a beneficial role as it has been associated with a decreased risk of developing car-diovascular disease, reduced blood pressure and low triglyceride levels [19].

- Matrix metalloproteinase 3 (MMP3): promoter polymorphism -1171 5A> 6A

Metalloproteinases are a family of enzymes important in the process of remodeling the

extracellular matrix and in the age-dependent stiffening of the arteries, and therefore involved in atherosclerotic etiology and in particular in the evolution of plaques. Ather-osclerotic plaques consist of two main components: a lipid-rich tissue and a collagen-rich sclerotic. Sclerotic plaques are considered less at risk as they are the most stable; on the contrary, the atheromatous "soft" component gives instability to the plaque and makes it more friable and therefore more at risk of thrombotic events. The role of metalloproteinases has been amply demonstrated in these mechanisms, as enzymes responsible for the reorganization of the plaques themselves. Recently, in the promoter area (in position -1171) of the MMP3 gene, a member of the MMP family, a polymorphism (5A> 6A) that influences the enzymatic activity of MMP3 has been identified. The 5A allele determines greater activity and has been associated with a greater risk of myocardial infarction, while the 6A allele determines a reduced activity of the enzyme and is a risk marker for arterial stenosis. For this polymorphism, experts suggest that the optimal genotype is a heterozygote for alleles (5A / 6A) [20].

- Endothelial oxide synthase (eNOS): polymorphisms -786 T> C, Glu298Asp and VNTR intron 4

In the vascular system, nitric oxide (NO) plays an important role by producing vasodila-tion, regulating blood flow and blood pressure, and conferring thrombo-resistance and protective properties to the endothelium of blood vessels. Endothelium-dependent vas-odilation is mediated by the release of NO produced by endothelial oxide synthetase (eNOS). A reduced synthesis of NO or its lower bio-availability could be the cause of the reduced endothelium-dependent vasodilation observed in the blood vessels of subjects with cardiovascular risk factors, such as active and passive smokers, patients with hy-pertension or hypercholesterolemia. The lack of NO-mediated effects can also predispose to the development of atherosclerosis. The -786 T> C polymorphism of the promoter region of the gene encoding endothelial oxide synthetase (NOS3) reduces endothelial NO synthesis, suggesting that carriers of this nucleotide variation are predisposed to the onset of coronary disease. But the most important indication is given by the fact that this reduction is exacerbated by cigarette smoking. The Glu298Asp missense variant, present at the level of exon 7 of the NOS3 gene, would act in synergy with the polymorphism of the promoter region, further increasing the risk of coronary disease. A rare VNTR polymorphism located in intron 4 of the NOS3 gene (Ins> Del Intron 4) represents a risk factor for myocardial infarction (MI). The frequency of this variant was shown to be significantly higher (approximately 7 times) in patients with MI without known secondary risk factors. This variant has also been associated with arterial stenosis, especially in association with the traditional risk factor for cigarette smoking [21-23].

- PARAOXONASE 1 (PON1): Gln192Arg polymorphism

Paraoxonase is a calcium-dependent glycoprotein, which circulates in high-density lip-oproteins (HDL), capable of preventing the peroxidation of low-density lipoproteins (LDL) and therefore counteracting the atheromatous process. The PON1 gene, encoding this protein, belongs to a multigenic family together with two other PON-like genes, called PON2 and PON3, all located on the long arm of chromosome 7. Several polymorphisms of the cluster of PON genes are known: the Gln192Arg polymorphism in the PON1

gene; it has been associated with cardiovascular risk, as it favors the atherosclerotic process [24].

- STEROL REGULATORY ELEMENT BINDING TRANSCRIPTION FACTOR 2 (SREBF2): Gly595Ala polymorphism

The SREBP family plays an important role in the regulation of cellular metabolism of cholesterol and fatty acids. A member of this family, SREBF2, plays a key role in choles-terol homeostasis, activating the absorption of plasma cholesterol mediated by the LDL receptor. A SNP polymorphism of the SREBF2 gene, Gly595Ala, which causes an amino acid change Gly> Ala at the level of codon 595, is associated with hypercholesterole-mia [25].

Protein	Mutation
APOA1	-75 G>A
Apo B	R3500Q
APOC3	C3175G/T3206G
APO E	E2, E3, E4
CETP	G279A/G1533A
GJPA 4	Pro319Ser
HMGCR	-911 C-A
LPL	C1595G
MMP3	-1171 5A>6A
eNOS	786 T> C, Glu298Asp, VNTR intron 4
PON1	Gln192Arg
SREBF2	Gly595Ala

Table 1: Metabolism of lipids

2.5 Metabolism and Obesity

Obesity is a complex disease due to genetic, environmental and individual factors with consequent alteration of the energy balance and excessive accumulation of adipose tissue in the body. Studies on families have always supported the hypothesis of a genetic in-fluence, responsible for the so-called metabolic anomalies that would facilitate the onset of obesity in the presence of high food availability and chronic sedentarism. Obesity represents an important risk factor for the onset of cardiovascular diseases (Table 2).

- 2B alpha adrenergic receptor: Ins> Del Codon mutation 299

The alpha2 adrenergic receptors influence energy metabolism through the inhibition of insulin secretion and lipolysis. The gene encoded for the alpha2B adrenergic receptor (ADRA2B) exhibits an Ins> Del Codon 299 polymorphism. The Del Codon 299 variant is very common in Caucasians (approximately 31%) and has been associated in vivo with reduced dilation of the brachial arteries and with a reduced flow of the coronary arteries. Furthermore, it is thought that this variant affects the basal metabolism and contributes to obesity [26].

- Beta 1 adrenergic receptor (ADRB1): Gly389Arg polymorphism

The beta 1 adrenergic receptors are the main cardiac receptors for Nor-Epinephrine and Epinephrine, which represent the most important mechanism by which blood flow is increased by the sympathetic nervous system. The ADRB1 gene, encoding the B1 adren-ergic receptor presents a polymorphism, Gly389Arg, consisting of the amino acid varia-tion Gly-Arg at the level of codon 389. The variant Arg389 is associated with a better re-ceptor function. This variant seems to predispose to heart attack and influence the ther-apeutic response to treatment with beta blockers. The Arg389 variant is also associated with hypertension [27,28].

- Beta 2 adrenergic receptor (ADRB2): Gly16Arg and Gln27Glu polymorphisms

The Arg16 allele of the ADRB2 gene determines an improvement in receptor sensitization and has been associated with hypertension. The simultaneous presence of the Arg16-Gln27 variants of ADRB2 leads to a reduced vasodilation mediated by the Beta 2 adrenergic receptor. The Glu27 variant is associated with an increase in the activity of the receptor, resulting in obesity and metabolic pathologies [29].

- Beta 3 adrenergic receptor (ADRB3): Trp64Arg polymorphism

Based on its biological role in lipid metabolism, the beta 3 adrenergic receptor is thought to be one of the genes that influences the accumulation of fat in the body. A missense mutation at codon 64 of the ADRB3 gene was associated with an increase in body mass index (BMI) [30].

- NEUROPEPTIDE Y: Leu7Pro polymorphism

Neuropeptide Y (NPY) plays an important role in the regulation of energy balance, me-diating the stimulation of food intake and energy accumulation. Among the many actions of NPY, vasoconstriction, blood pressure regulation, cholesterol metabolism and the pathogenesis of atherosclerosis are also re-compressed. A rare polymorphism of the NPY gene, Leu7Pro, has been associated with high amounts of total and LDL cholesterol, especially in patients with obesity. Furthermore, this polymorphism is a marker for the risk of hypertension and arteriosclerosis [31].

- Peroxisome proliferator-activated receptor - gamma (PPARG): Pro12Ala polymorphism

PPAR-gamma (PPARG) is a receptor that is known to play an important role in stimu-lating the body's natural process underlying the regulation of lipid and carbohydrate metabolism, increasing insulin sensitivity. High blood pressure, lipid abnormalities, in-sulin resistance and central obesity are the main components of the metabolic syndrome, which commonly preludes cardiovascular disease and type 2 diabetes. The characteristic of the metabolic syndrome is to combine major cardiovascular risk factors including central obesity, insulin resistance, high blood pressure and blood lipid abnormalities. Almost a quarter of the world population is affected by metabolic syndrome. Up to a maximum of 80% of the nearly 200 million adults in the world affected by diabetes die of cardiovascular diseases. People with metabolic syndrome are at greater risk than others as they are twice as likely to die from a heart attack and three times as likely to die from a stroke. Some studies support a beneficial role of the Pro12Ala polymorphism, which is associated with a reduced transcription of the PPARgamma2 gene. Furthermore, this polymorphism is associated with a

decrease in the body mass index (BMI), a reduction in insulin levels, an increase in HDL levels and improved insulin sensitivity. Hence, the Pro12Ala polymorphism decreases the risk of type II diabetes mellitus [32].

Protein	Mutation
2B alpha adrenergic receptor	299
ADRB1	Gly389Arg
ADRB2	Gly16Arg, Gln27Glu
ADRB3	Trp64Arg
NPY	Leu7Pro
PPARG	Pro12Ala

Table 2: Metabolism and obesity

2.6 Metabolism of Homocysteine

In recent years, more and more scientific evidence has been accumulating on how clinically increased levels of homocysteine represent a new independent cardiovascular risk factor that can be combined with other traditional risk factors or that can enhance their deleterious effects on the arterial wall. Cigarette smoking and the dietary intake of folate and vitamin B12 are among the main determinants of plasma homocysteine concentrations. Homocysteine seems to induce vascular damage by interfering with the production of nitric acid by the endothelium, causing hyperplasia of smooth muscle cells and increasing the production of free radicals with consequent oxidative damage and li-pid peroxidation (thus favoring the formation of atherosclerotic plaque) as well as by interfering with platelet function and increasing the tendency to thrombosis. Hyperho-mocysteinemia also has important implications in human reproduction related to the moment of conception (repeated abortions), the state of pregnancy (vascular-dependent diseases such as preeclampsia, fetal growth failure, placental abruption) and menopause (Table 3).

- Cystathionine Beta Synthase (CBS): C699T and T1080C polymorphisms

CBS is an enzyme necessary to convert homocysteine into Cystathione. This enzyme re-duces homocysteine levels. It has been shown that two polymorphisms of the CBS gene (C699T and T1080C) cause an increase in the activity of the enzyme, reducing the amount of homocysteine in the blood. These polymorphisms are associated with a reduced risk of developing coronary heart disease [33].

- MTHFR (Methylenetetrahydrofolatoreductase): C677T and A1298C polymorphisms

Methylenetetrahydrofolatoreductase (MTHFR) is an enzyme involved in the transfor-mation of 5-10 methylenetetrahydrofolate into 5 methyltetrahydrofolate which serves as a methyl donor for the remethylation of homocysteine to methionine through the inter-vention of vitamin B12. Rare mutations (transmitted in an autosomal recessive manner) can cause severe MTHFR deficiency with enzymatic activity less than 20% and

the ap-pearance of homocysteinemia and homocystinuria and low plasma levels of folic acid. The clinical symptoms are severe with delayed psycho-motor development and massive thrombotic phenomena. Alongside severe MTHFR deficiency, a common genetic poly-morphism has been identified, due to the substitution of a C (cytosine) in T (thymine) at nucleotide 677 (C677T), which causes a substitution of an alanine in valine in the final protein and a reduction of the enzymatic activity of MTHFR equal to 50%, up to 30% in conditions of exposure to heat (thermolabile variant). This variant involves elevated levels of homocysteine in the blood especially after oral methionine loading. This poly-morphism, however, does not affect homocysteine levels if the folate content of the diet is high, but is associated with hyperhomocysteinemia if the folic acid content of the diet is low. Similarly, individuals carrying the 677CT variant are also those who respond best when subjected to dietary supplementation with folate. The gene frequency in Europe of the mutation is 3-3.7% which leads to a condition of heterozygosity in about 42-46% of the population and homozygosity of 12-13%. Recently, a second mutation of the MTHFR gene (A1298C) has been associated with reduced enzymatic activity (approximately 60% individually; approximately 40% if present in association with the C677T mutation). This mutation, in patients carrying the C677T mutation, causes an increase in blood levels of homocysteine. Increased levels of homocysteine in the blood are now considered a risk factor for vascular disease (arterial thrombosis), possibly through a mechanism mediated by sulfhydryl groups on the endothelial wall of the vessels. Furthermore, in conditions of dietary folic acid deficiency, the thermolabile variant of MTHFR leads to very low levels of folic acid in the plasma and is therefore a risk factor for neural tube defects in pregnant women [34-38].

- Methionine synthetase gene (MTR): A2756G polymorphism

The MTR gene encodes an enzyme that is involved in the conversion of homocysteine into methionine. The A2756G polymorphism increases the activity of this enzyme, affecting the blood levels of folate and homocysteine. Reduced homocysteine levels reduce the risk of onset of cardiovascular diseases. Furthermore, the presence of the A2756G polymorphism has been shown to decrease the likelihood of neural tube defects during pregnancy and a decreased risk of venous thrombosis [39].

- Methionine synthetase reductase (MS_MTRR): A66G polymorphism

Methionine synthetase reductase is an enzyme necessary for the formation of a vitamin B12 derivative. This enzyme is essential to maintain an adequate amount of cellular vitamin B12, methionine and folate, and to keep homocysteine levels low. The A66G polymorphism is associated with an increased risk of cardiovascular disease, independ-ent of homocysteine levels. It has also been shown that this polymorphism increases the risk of neural tube defects, spina bifida and Down syndrome during pregnancy [40].

Protein	Mutation
CBS	C699T and T1080C
MTHFR	C677T and A1298C
MTR	A2756G
MS_MTRR	A66G

Table 3: Metabolism of Homocysteine

9. Inflammatory response

It has been known for many years that the deposition of fats derived from cholesterol in the vessel wall induces the activation of cells normally present in this area of the vessels called macrophages. After ingestion of this material, the macrophage is activated and induces an abnormal inflammatory response in the vessel wall which over time leads to the formation of atherosclerotic plaque and the vessel changes typical of atherosclerosis. Therefore, components and factors with regulatory activity on the inflammatory response play an important role in the development and clinical manifestation of complications of atherosclerosis, such as myocardial infarction (Table 4).

- Interleukin-1B (IL-1B): polymorphism -511 C-T

The interleukin-1 gene (IL-1) is located on chromosome 2 where there is an aggregate of genes that codes for both IL-1b, IL-1a and for the receptor of these two molecules. IL-1 is a pluripotent cytokine, that is capable of carrying out and regulating many immune func-tions and is mainly involved in the activation of inflammatory responses. In particular, IL-1b is also released into the bloodstream by exerting widespread actions in the body. In fact, it is one of the factors capable of inducing fever, sleep, anorexia and hypotension. This interleukin is important in the pathogenesis of myocardial infarction as it stimulates macrophages and endothelial cells to release tissue factor (TF), a powerful thrombus in-ducer. The polymorphism present on the IL-1b promoter in position -511 consists in the replacement of a C (cytosine) with a T (thymine). The presence of the T allele in conjunc-tion with certain alleles of other polymorphisms on other genes increases the risk of de-veloping the disease, therefore, subjects carrying this genotype, especially when present together with other genotypes, are more likely to have a heart attack myocardium com-pared to non-carriers. On the other hand, in subjects with protective IL-1 beta polymor-phism, blood clotting is induced to a much lesser extent, thus reducing the likelihood of being exposed to the risk of heart attack or stroke [41].

- Interleukin-6 (IL-6): G-634C and G-174C mutations

The interleukin-6 (IL-6) gene is located on chromosome 7 and encodes the protein of the same name. IL-6 is a pleiotropic cytokine, capable of performing many functions; it gen-erally has a pro-inflammatory action, therefore it induces inflammatory responses. IL-6 is involved in the regulation of both acute and chronic inflammatory responses and in the modulation of specific immune responses. It is now known that inflammation plays a major role in the pathogenesis of atherosclerosis since atherosclerotic plaques and asso-ciated lesions have an infiltrate of activated immune cells and an increased synthesis of inflammatory molecules. In this regard, IL-6 was one of the first cytokines

studied in cardiovascular diseases as it promotes the formation of atheromas, dyslipidemia and hypertension. Various studies that have followed populations over time have proposed using the plasma level of this protein as a predictive marker for heart attack. In fact, it has been observed that the blood levels of IL-6 increased long before the clinical manifestation of the heart attack and correlated with the incidence of the disease. The IL-6 gene contains various polymorphisms including one present in the promoter in position -174 which consists in the replacement of a G (guanine) with a C (cytosine), and another present in position -634, also characterized by replacement of a G with a C. Studies conducted on a group of patients with myocardial infarction and on a group of healthy subjects without cardiovascular disease have shown that these polymorphisms represent a risk factor for heart attack. That is, carriers of the mutated C allele are more likely to be affected by this pathology than non-carriers. Furthermore, the presence of these alleles also correlates with higher plasma levels of IL-6 [42-45].

- Interleukin-10 (IL-10): G-1082A mutation

Interleukin 10 (IL-10) is a gene located on chromosome 1 and encodes the protein of the same name. It is an anti-inflammatory molecule that means it inhibits the release of pro-inflammatory cytokines during the development of inflammatory responses. It is secreted by T lymphocytes, monocytes and macrophages. This molecule regulates in-flammatory responses and has immunosuppressive activity. Since the presence of a poorly controlled inflammatory response promotes cardiovascular diseases, IL-10, having an immunosuppressive action, plays an important and protective role in the pathogenesis of cardiovascular diseases. Many studies have studied the polymorphism present in the promoter region of the IL-10 gene at position -1082. This polymorphism consists in the replacement of a G (guanine) with an A (adenine). It is useful to remember that in vitro studies have suggested that the presence of the A allele is associated with a lower production of the IL-10 molecule. It was found that the presence of the AA genotype in-creases the risk of developing myocardial infarction, in other words carriers of this gen-otype have a higher risk of developing cardiovascular diseases than non-carriers [46].

- Tumor necrosis factor alpha (TNFα): polymorphism -308 G-A

The tumor necrosis factor alpha (TNFα) gene is located on chromosome 6 and encodes the protein of the same name. TNFα is a pleiotropic pro-inflammatory cytokine that is capable of performing numerous regulatory functions on immune responses. TNFα is also an important mediator of both acute and chronic inflammatory responses. The concentration of TNFα increases during the vascular damage produced by the formation of thrombi This factor promotes damaged endothelial cells by stimulating them to produce adhesion molecules. Therefore, by promoting adhesion to endothelial cells, TNFα acts as a factor promoting atherogenesis and vascular damage causing heart attack. The TNFα gene has various polymorphic sites, including a polymorphism present in the promoter region of the gene at the -308 position. This polymorphism consists of a substitution of a G (guanine) with an A (adenine). In vitro studies have shown that the presence of the A allele is associated with a greater production of the molecule itself. Our clinical patho-physiology studies indicated that this polymorphism was found to be a marker for car-diovascular disease. Analyzing the data obtained by genotyping a group of patients with myocardial infarction and its control group, it can be

stated that this genotype is a marker of risk of myocardial infarction [47-49].

Protein	Mutation
IL-1B	-511 C-T
IL-6	G-634C, G-174C
IL-10	G-1082A
TNFα	-308 G-A

Table 4: Inflammatory response

2.8 Antioxidant activity and Detoxification

The antioxidant activity helps fight the damage caused by free radicals, (RL) which represent the waste of the reactions of the human metabolism. RLs are practically the product of the metabolic biotransformation that our body practices through the processing of the foods we eat every day. These RL molecules are highly reactive and can induce premature aging of tissues, from the skin to internal organs, veins and arteries, cardiovascular diseases such as stroke and heart attack, up to highly degenerative dis-eases such as some types of cancer. Certain polymorphisms present in specific genes can alter the production and function of antioxidant enzymes (Table 5).

- Manganese dependent superoxide dismutase (MnSOD): C (-28) T and T175C polymorphisms

Manganese dependent superoxide dismutase (MnSOD), a mitochondrial antioxidant enzyme that catalyzes the conversion of superoxide radicals to hydrogen peroxide. MnSOD is encoded by the SOD2 gene located at the 6q25 locus. The gene has two poly-morphisms, C (-28) T and T175C: the C (-28) T polymorphism influences the intracellular distribution of the enzyme, preventing the latter from entering the mitochondria. This polymorphism has been associated with a higher risk of developing some pathologies, in particular cardiovascular ones. However, it is the absence of polymorphism, and not its presence, that favors the development of these pathologies. The favorable effect of the presence of this polymorphism is due to the fact that the enzyme remains functional, but distributed within the cell instead of being concentrated in the mitochondria. The risk of the onset of the aforementioned diseases decreases with a greater introduction of foods rich in antioxidants into the diet. The T175C polymorphism, on the other hand, reduces the stability of the active enzyme by about 3 times [50].

- Superoxide Dismutase (SOD3): C760G polymorphism

SOD3 is the main antioxidant enzyme of the blood vessel walls. The highest levels of SOD3 are found in the heart, placenta, pancreas and lungs. Moderate levels of SOD3 are also found in the kidneys, muscles and liver. It has been shown that the C760G poly-morphism determines the release of the enzyme SOD3 from the walls of the blood vessels and is associated with a reduction in tissue antioxidant activity. This can contribute to the development of coronary artery disease [51].

- Glutathione S-transferase

Glutathione S-transferases (GSTs) are a family of detoxifying isoenzymes that catalyze the conjugation of various toxic molecules with glutathione making them less reactive and more easily eliminated from the body. These enzymes are encoded by polymorphic genes comprising 5 classes: alpha, Pi, Mu, Theta and Zeta.

- Glutathione S-transferase P1 (GSTP1): I105V and A114V polymorphisms

Recently, two common polymorphisms of the GSTP1 gene have been associated with a substantial decrease in the activity of the enzyme. One of these polymorphisms, I105V, is characterized by a single A> G substitution at the level of nucleotide 313 and determines at the level of the protein an amino acid substitution alanine> valine at position 105; the other polymorphism, A114V, is characterized by a single C> T substitution at nucleotide 341 and determines an amino acid substitution isoleucine> valine at position 114 at the protein level. The variant GSTP1 105Val has a frequency of 33% among the population Caucasian with 14% homozygotes [52].

- Glutathione S-transferase mu, M1 (GSTM1): gene deletion

This polymorphism, characterized by the deletion of most of the coding region of the gene, causes a loss of enzyme functionality [53].

- Glutathione S-transferase theta, T1 (GSTT1): gene deletion

This polymorphism, characterized by the deletion of most of the coding region of the gene, causes a loss of enzyme functionality. It has also been associated with an increased risk of lung, larynx, bladder, prostate and cervical cancer [54].

Protein	Mutation
MnSOD	C (-28) T and T175C
SOD3	C760G
GSTP1	I105V and A114V
GSTM1	delection
GSTT1	delection

Table 5: Antioxidant Activity and Detoxification

2.9 Bone Metabolism and Osteoporosis

Osteoporosis is the most frequent metabolic disease of the skeleton, characterized by a reduction in bone mass and an alteration of the microarchitecture which results in an increase in fragility and susceptibility to fractures. A familiarity with osteoporosis has been verified for some time, however, studies aimed at identifying and characterizing the genetic components of this disease have only begun in recent years. The peak bone mass observed between 20 and 30 years of age is largely determined by genetic factors as well as the rate at which bone mass decreases following menopause or aging. Furthermore, during life, environmental risk factors can accumulate which can be decisive for the onset of the disease. Thus the pathogenesis of osteoporosis is the result of complex interactions between ge-netic predisposition and environmental risk factors.

Genetic factors play an important role in the pathogenesis of osteoporosis and are represented by the pool of genes that regulate the expression of characters related to the development of the disease (bone mass and microarchitecture). Environmental factors include eating habits (calcium and vitamin D intake), consumption of alcohol, tobacco and coffee, physical activity, taking drugs that interfere with phospho-calcium metabolism and above all exert a selective effect on the genetic characteristics of the individual. In fact, although various environmental influences on the determination and maintenance of bone mineral density (BMD) are evident, studies on twins and osteoporotic families indicate that the genetic contribution to the pathogenesis of osteoporosis is responsible for 75-85% of the inter-individual variability of BMD (Table 6).

- Genetic polymorphisms associated with osteoporosis

The characterization of genetic markers related to the inheritance of low bone mineral density could allow the early identification of individuals susceptible to developing os-teoporosis. In this way, targeted prevention could be activated with specific therapies and lifestyle changes, such as to minimize the environmental risk in individuals genetically predisposed to develop the disease.

Since 1995, several studies have been initiated to identify and characterize polymor-phisms in various genes related to bone metabolism: these analyzes are aimed at high-lighting correlations between the presence of a specific allelic variant and a situation of reduced bone mass density. Several polymorphisms have been identified and analyzed so far: within the genes that code for the vitamin D receptor (VDR), Collagen IA1 (COLIA1), calcitonin receptor (CTR) and estrogen receptor (ESR). The results obtained from these studies allow us to state that osteoporosis is a polygenic disease, therefore a more certain determination of the predisposition to the disease requires the analysis of the different polymorphisms.

- Vitamin D receptor (VDR): Fok1, BsmI, and TaqI polymorphisms

Vitamin D promotes intestinal and renal absorption of calcium and is essential for the development and maintenance of bone mass. Vitamin D is also involved in the control processes of cell proliferation and differentiation, as well as in immuno-modulation. In the immune system, for example, vitamin D promotes the differentiation of monocytes and inhibits the proliferation of lymphocytes through the secretion of cytokines such as IL-2, IL12 and interferon "γ". In some types of carcinoma cells, vitamin D has shown an-tiproliferative activity. The effects of Vitamin D are mediated by its nuclear receptor (VDR), which forms a heterodimeric complex with the retinoic acid receptor and interacts with transcription factors. VDR (12q12-14) encodes a 427 amino acid (aa) protein, which regulates the transport and homeostasis of calcium and has been proposed as the locus with the greatest genetic effect on BMD in association studies. There are several poly-morphic sites in the 3' region of the human VDR gene identified by the restriction en-donucleases TaqI and BsmI, and another polymorphic variant, recognized by FokI, at the presumed transcription start codon in exon 2. The alleles are respectively called Tt, Bb and Ff: lowercase letters identify the presence of the restriction site and capital letters indicate the absence of this site. These polymorphisms can affect the response to various dietary components with possible risks of developing pathology. A functional involvement of the VDR alleles in calcium homeostasis and bone

mineralization has now been widely demonstrated. The initial studies made it possible to find the interaction between the VDR gene, calcium absorption and calcium levels in the diet. Allelic variations of the VDR gene account for 70% of the genetic effects on bone density. The Fok1 polymorphism consists of a T-C nucleotide substitution at the translation initi-ation codon of the VDR gene (ATGÂ®ACG). This polymorphism determines the trans-lation of three amino acids from the starting site of the translation of the gene with con-sequent alteration of the relative protein, lacking in three amino acids. The T nucleotide is also referred to as the f allele, while the C nucleotide is referred to as the F allele. The combination of these alleles can produce the ff (TT), Ff (CT) and FF (CC) genotypes. The FF genotype (short form) causes an increase in transcription activation. The ff genotype has been associated with low lumbar BMD in postmenopausal, Japanese, North American, and Italian Hispanic-American women. Environmental factors, such as daily calcium intake, can also modulate the effects of FokI genotypes on BMD. The results obtained from all these association studies show that VDR polymorphisms alone are not useful genetic markers to assign the risk of Osteoporosis, although they are very useful in explaining the variability of BMD observed in the population. The BsmI polymorphism, located in intron 8 of the VDR gene and consisting of a nucleo-tide variation A-G, is instead associated with the variation in the stability of the transcript and a decrease in the value of the BMD. Nucleotide A is also referred to as allele B, while nucleotide G is termed allele b. The combination of these alleles can produce the geno-types BB (AA), Bb (AG) and bb (GG). The highest density values were found to be borne by allele b, while the less frequent allele B was associated with lower BMD values. Hence the BB genotype would predispose to a low level of bone mass. Furthermore, some studies have shown that the BB genotype predisposes to a reduced absorption of calcium in the intestine. The TaqI polymorphism, located in exon 9 of the VDR gene, at the level of codon 352, consists of a T-C nucleotide variation. The T nucleotide is also referred to as the T allele, while the C nucleotide is referred to as the t allele. The combination of these alleles can produce the TT (TT), Tt (TC) and tt (CC) genotypes. This polymorphism has been asso-ciated with an increase in bone cell turnover resulting in an increased risk of decreased BMD and osteoporosis. Several other pathologies have been related to the association with the aforementioned polymorphisms in the VDR gene, such as to be able to influence the expression or function of the protein. In particular, these polymorphisms (Fok1, BsmI, and TaqI), can affect the response to various dietary components with possible risks of developing pathology. In the literature, some works are known that correlate the associ-ation of the VDR Fok1 polymorphism with the FF genotype, with the risk of developing colon cancer, in relation to the intake of calcium and fat in the diet. In particular, it has been shown that, although dietary calcium or fat do not normally correlate with the risk of developing colon cancer in subjects with the FF genotype, in those with the multiple allelic combination ff / Ff genotype, a decreased calcium intake or fat in the diet would increase this risk. For individuals with the ff genotype and a diet low in fat and calcium, the risk of developing colon cancer was approximately 2.5 times greater than for others [55-56].

- Collagen type I (COLIA1): intron 1 polymorphism 2046G-T

Type I collagen is the major organic component (90%) of the bone matrix. In osteoporotic subjects the collagen chains are normal, however a polymorphism has been identified in the regulatory site of the COLIA1 gene which appears to be more frequent than in normal controls. This polymorphism, found at the binding site for the transcription of factor SP1 in the first intron of COLIA1, is associated not only with bone mass but also with osteo-porotic fractures in several Caucasian populations. This causes COLIA1 to acquire par-ticular interest, since the association with fractures is stronger than that between genotype and bone mass. It should also be emphasized that this polymorphism is almost absent in the populations of Asia and Africa, where the incidence of osteoporotic fractures is lower. Several studies on COLIA1 show that the genetic effect of COLIA1 is strongly associated with reduced bone mass values and the relationship appears closer at the level of the spine. In particular, the T (s) allele, both in G / T (Ss) and in T / T (ss) homozygosity, appears more frequent in subjects with severe osteoporosis associated with vertebral fractures. Therefore it has been suggested that COLIA1 may predispose to fractures by influencing other determinants of fracture risk such as bone quality or skeletal geometry. It cannot be excluded that those most at risk with the ss genotype have impaired collagen production with a consequent reduction in peak bone mass and probably in the thickness of the trabeculae. The hypothesis that the ss genotype is associated with an altered pro-duction of collagen is also in agreement with previous histomorphometric data according to which subjects with vertebral fractures have a reduced capacity for bone formation [57].

- Calcitonin receptor (CTR): PRO463LEU polymorphism

Another gene more recently studied in osteoporosis is that of the calcitonin receptor (CTR). Calcitonin is a hormone involved in bone resorption and acts through specific receptors present in large numbers on osteoclasts. A polymorphism of the CTR gene has been identified consisting of a C-T nucleotide variation at the level of codon 463 (PRO463LEU). This mutation has been associated, under homozygous conditions (genotype TT, 463LEU) with a reduction in bone mass [58].

- Estrogen receptor 1 (ESR1): PvuII (IVS1-397 T / C) and XbaI (IVS1-351 A / G) polymorphisms

Estrogens are essential for the acquisition of peak bone mass in both sexes and for its maintenance in adults. Pathological conditions associated with premature estrogen defi-ciency accelerate bone loss. Estrogen deficiency is the main cause of postmenopausal os-teoporosis and also plays an important role in senile osteoporosis, causing in both cases a higher incidence of fractures due to bone fragility. The two estrogen receptor isoforms (ER-beta and ER-alpha) are encoded by two different genes (ESR2 and ESR1) with specific tissue distribution and have different capabilities in binding the ligand (estrogens and anti-estrogens) and in activating the transcription of target genes. Several observations show the involvement of these receptors in the determination of BMD in both sexes. Several polymorphisms have been described in the ESR1 gene (6q25), but all association studies focus on 2 of them, located at intron 1 level (recognized by PvuII and XbaI and called respectively Pp and Xx, based on the presence or absence of the restriction site). The PvuII polymorphism is located in intron 1 of the ESR1 gene and consists of a T / C nucleotide variation in position -397. The T nucleotide is also referred to as the p allele, while the C nucleotide is

referred to as the P allele. The combination of these alleles can produce the pp (TT), Pp (CT) and PP (CC) genotypes. The PP genotype is associated with a receptor dysfunction with reduced response to endogenous estrogens, a lower BMD and an increased risk of osteoporosis. The XbaI polymorphism is located in intron 1 of the ESR1 gene and consists of a nucleo-tide variation A / G in position -351. Nucleotide A is also referred to as the x allele, while nucleotide G is referred to as the X allele. The combination of these alleles can produce the genotypes xx (AA), Xx (GA) and XX (GG). An association between the XX genotype and a greater risk of fracture was found through a BMD-independent mechanism [59,60].

Protein	Mutation
VDR	Fok1, BsmI, TaqI
COLIA1	2046G-T
CTR	PRO463LEU
ESR1	PvuII, XbaI

Table 6: Bone Metabolism

2.11 Matching the diet to individual microbiome profile

The human body consists of at least 100 trillion microorganisms, the majority of which reside in the gut. These microorganisms, including bacteria, viruses, fungi, and a few other single-cell organisms, are collectively called microbiota, sometimes referred to as the microbiome [61]. The composition of the microbiota can vary among individuals [62]. It is believed that this interpersonal variation is due to complex interaction of the genetics and environmental factors, such as, diet, lifestyle, physical activity, etc. Microbial organisms interact with each other and with the host, contributing to both healthy functions and disease [63,64]. In a healthy organism, there is a symbiotic relationship between the human host and the microbiome. The former provides nutrients from the food; the latter facilitates digestion and absorption and synthesizes essential vitamins. In addition, microbiome can influence human health by secreting products of bacterial metabolism, called metabolites [65,66]. These are small chemical molecules that can travel in the intestinal lumen and be beneficial or detrimental to intestinal function. In patients with inflammatory bowel diseases (Crohn's and ulcerative colitis) the microbial balance is disrupted and there is an abundance of certain bacterial and fungal species. However, it remains unclear whether the changes in the microbiome are a result of chronic in-flammation in IBD or whether it is the microbiome disbalance that causes the onset of IBD [67]. From recent studies focused on co-evolution of humans and their gut microbiota, it is clear that diet and lifestyle affect the composition of microbiota and play a role in human health. Westernization of diet leads to loss of bacterial diversity and our microbiome loses the ability to digest plant-derived fiber and to produce beneficial metabolites such as anti-inflammatory short-chain fatty acids [68-73]. Several studies confirmed association between a high animal protein diet and fat intake, with increased risk of developing

IBD; while a diet rich in olive oil, fish, vegetable, fruit, grains, and nuts has the opposite association, i.e. fewer cases of IBD were reported among people consuming the latter type of diet [74-76]. Multiple studies are ongoing to establish which types of diet can have a therapeutic effect on intestinal health in general and specifically in IBD. From an observational study that compared omnivore, vegetarian or vegan diets it was reported that Mediterranean diet is associated with a healthier microbiome-related profile. Exclusive enteral nutrition (EEN) induced remission of Crohn's disease and is therefore the firstline therapy in many parts of the world [77,78]. However, the researchers could not confirm that this improvement is due to changes in microbiota and that the microbiome can be modified by nutrition therapy. Thus, the mechanism through which nutritional therapies work remains unclear, as does the role of microbiome in the progression of IBD and whether specific nutrients can help to reinstate a healthy microbial balance in the gut of an IBD patient [79,80]. Overall the efficacy of dietary therapies is still controversial. In order to design new dietary therapies and ex-pand our understanding of the causal relationship between the microbiome and IBD, we first need to obtain more evidence of the effects of individual nutrients on microbiota in properly designed clinical trials. There are a few critical factors to be considered in nutritional studies [81]. Clinical trials need to focus on testing individual nutrient, by giving or omitting this nutrient from otherwise homogeneous diet, without patients knowing which type of diet they are getting to avoid the placebo effect. This type of clinical study is called blinded randomized control trial. In addition, the number of patients enrolled in the study should be large enough to produce statistically significant results. If the subject sample size is too small the effects of diet on the microbiome can be hidden by high in-terpersonal variability. Namely, one nutrient can have different effect on different baseline microbiomes and if there are not enough samples of each kind, scientist can't see a pattern of cause and effect and thus the results of the study will be inconclusive. What can help to minimize the variability of baseline microbiome and the variation in the metabolic response to a diet is if the criteria for patients' enrollment are uniform: close age, similar health status, and lifestyle. It would be ideal to follow the clinical and biological parameters (biomarkers) as well, such as host metabolism, inflammation, and gut microbiota composition, to quantify the effect of nutrition on the disease-relevant bio-logical processes, to monitor the response to different doses of nutrient and to different timing of administration. This will also allow excluding patients with unique baseline parameters which can potentially amplify or counteract the effects of nutritional therapy. Screening for these biomarkers before enrollment in a clinical study or clinical trial may increase the costs of the study but will enable more consistent data to be obtained from a small group of patients. During the study, monitoring the nutrient intake though questionnaires, measurement of the nutrient level in biological fluids should be done to endure ensure compliance with the standard research protocol. While studying separate nutrients, scientist also recognize that habitual consumption of healthy and diverse diet is important to shape the microbiome and to maintain its healthy state. Different people may have distinctive metabolic response to the same food. It is likely that through metabotyping - grouping individuals with similar metabolic profile- more effective, personalized nutritional therapy can be achieved. Scientists are trying to apply machine learning (complex computer algorithms) to design

personalized healthy nutrition based on the biomarkers of the microbial composition, anthropological characteristics, metabo-lites, dietary habits, physical activity, and lifestyle [82].

3. Conclusions

Precision nutrition represents an interesting approach for the prevention and treatment of some of the major chronic diseases. In recent years, numerous genetic variants able to influence the metabolic profile have been identified, however it is still premature to at-tribute the risk of inducing diseases characterized by complex, multifactorial, largely unknown pathogenesis to individual genetic variants. The studies currently available, although very suggestive on the pathophysiological level, have not yet provided transferable results on a clinical level and at the moment there are no validated nutrigenetic tests to be used in practice. Evidence of efficacy and safety aimed at establishing the incremental value of the nutrigenetic approach compared to the classic one is still weak and based on observational or retrospective studies with a low level of reproducibility [83]. As you can easily understand, the commercial potential of this sector is enormous and the market has already activated in this sense, in fact, there are several services aimed at consumers which, through DNA analysis (just send a saliva sample), they can trace back to their specific "sensitivity" towards many nutrients, such as: alcohol, coffee, carbohy-drates, saturated fats, omega3, antioxidants, vitamin D, etc. Certainly the potential is compelling and research must continue to produce knowledge to assert the beginning of a new era of nutrition. In summary, development of personalized nutrition based on the features of the micro-biome is currently being attempted. Despite the aforementioned challenges, modulating and manipulating the gut microbiome with a personally designed dietary intervention to induce changes in its composition and functions is surely a promising application for both therapeutic and preventive clinical strategies [81].

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