Nutri (Epi) Genomics and Metabolic Syndrome

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The metabolic syndrome is a cluster of risk factors such as obesity, insulin-resistance, hypertension, dyslipidemia, inflammation associated with an increased risk of type 2 diabetes mellitus (T2DM) and cardio vascular diseases (CVD). Rapid globalization, urbanization and industrialization have spawned epidemics of metabolic syndrome and it has become one of the major threats among adolescents and children. It is influenced by the interaction of genes, nutrition, environment, and lifestyle. The technological advances in life sciences have led to the realization that certain nutrients are not only essential, but also specific quantity of each nutrient is necessary for optimal health. Therefore, it is important to understand the biological impact of gene–nutrient-disease interactions, which will provide an insight into the pathogenesis and progression of metabolic syndrome. The present review is focused on the role of gene-nutrient interactions (Nature vs Nurture) towards the development of metabolic syndrome and associated co-morbidities and its epigenetic regulation.

Keywords: Epigenomics; Nutrigenomics; Gene-nutrient Interactions; Metabolic Syndrome; Obesity; Type 2 Diabetes Mellitus; Cardio Vascular Diseases; Hypertension

Introduction

Nutrition clearly had a predominant and recognizable role in health and disease since the times of the renowned Greek physician Hippocrates. However, our understanding of diet and its effects on health has evolved with time from crude associations to conclusive facts (Mutch et al., 2005). The technological developments in life sciences and the advent of modern science, have led to the realization that certain nutrients are not only essential, but also specific quantity of each nutrient is necessary for optimal health. Further, it is now realized that the nutrient/diet can directly contribute to diseases. Advances in genome sequencing and complete elucidation of the Human Genome Project (HGP) has led to questions, whether the interaction between genes/genotypes and bioactive compounds of nutrient/diet could positively or negatively influence an individual’s health (Sales et al., 2014). Bioactive compounds in the diet and genetics are two major factors which determine the development of metabolic syndrome that comprises cardiovascular diseases, diabetes, hypertension and obesity (Mutch et al., 2005; Gaboon, 2011). Adequate amount of nutrients indeed prevent/delay the development of metabolic syndrome. To understand these interactions between genes and nutrients, the term “Nutrigenomics” was coined. Nutrigenomics implies the use of biochemistry, physiology, nutrition, genomics, proteomics, metabolomics, transcriptomics and epigenomics to seek and explain the existing reciprocal interactions between genes and nutrients at a molecular level. Nutrigenomics and nutrigenetics are two sides of the same coin. While the former describes how nutrients

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affect metabolic pathways and homeostatic control epigenetically, the latter tries to understand how the genetic make-up of an individual influences their response to diet. The discovery of these gene-nutrient interactions would aid in personalized diets according to individual’s genotype (Sales et al., 2014). Further, understanding of gene–nutrient interactions would help in mitigating the symptoms of existing diseases and/or to prevent future illnesses, especially in the area of non-transmissible chronic diseases (NTCDs), which are currently considered as an important global public health problem.

**Nutrition, Genomics and Epigenomics**

Nutrigenomics is the science of the effect of nutrients and bioactive components on gene expression and helps one understand how diet regulates gene function (transcription and translation), DNA methylation, proteome and metabolome (i.e. in the simplest terms: diet → gene interactions) which can be studied independently or in an integrated manner, to diagnose health status and/or to understand disease trajectory (Elliott and Johnson, 2007; Gaboon, 2011). Recent developments in nutrigenomics has established the effects of ingested nutrients and other food components on gene expression and its regulation in order to delineate the dietary components having beneficial or detrimental effects on health. It would also determine the individual nutritional requirements (personalized diet), association between diet and metabolic syndrome which is essential to understand the aetiology of type-2 diabetes, obesity and cardiovascular disease (CVD). Although humans have 99.9% identical gene sequences; 0.1% genetic variation makes an individual unique from others with respect to their phenotype, susceptibility to disease or health and their differential responses to nutrients (Elliott and Johnson, 2007). Nutritional factors strongly affect the association of common gene variants with multi-factorial chronic conditions. Evidently, major metabolic diseases are closely inter-related, often through obesity, caused mainly by dysregulation of energy homeostasis. Under certain circumstances, diet can be a risk factor for some individuals, while in others it may be beneficial (Rajoka et al., 2012). On the other hand, nutrigenetics is to elucidate the effect of genetic variation on the interaction between diet & disease, for example; phenylketonuria (PKU) and describes how the genetic make-up of a particular individual co-ordinates their response to various dietary nutrients (i.e. in the simplest terms: gene → diet interactions) (Mutch et al., 2005; Berna et al., 2014). Further, it also shows why and how people respond differently to the same type of nutrient. It has the potential to provide scientific evidence for personalized dietary recommendations concerning health management based on the individual’s genetic makeup. Generally dietary bioactive compounds act on the genome directly or indirectly and alter gene expression. Some diet-regulated genes are likely to play a role in the onset, progression, and/or severity of metabolic syndrome. Further, dietary interventions based on knowledge of nutritional requirement, nutritional status and genotype could be used to prevent, mitigate or cure metabolic syndrome.

Epigenetics is defined as the study of changes in organisms caused by the modification of gene expression, rather than the alteration of the genetic information itself. Epigenetic regulation is an essential process in normal development that occurs all through life. Further, it has been explained as the study of external or environmental factors that turn genes on and off and affect how cells read genes. The excitement about epigenetics is how the gene expression stably reprogrammed in response to transient external stimuli. It is required to achieve stable expression or repression of genes in specific cell types or at specific time-points and constitutes the link between genotype and phenotype. Most importantly, it could be inherited between generations steadily by mitosis and meiosis through cell differentiation. Epigenetic conditions can illustrate the reason why an organism produces many different cell types during its development, despite the fact that most of the cells in a multi-cellular organism share the same genetic information. Epigenetic change is a regular and natural occurrence but can also be influenced by several factors including diet, environment/lifestyle, age and disease state. Studies have shown that the effects of nutrition/diet could be passed on epigenetically to the offspring add weight to the idea that histones act as metabolic sensors, converting changes in metabolism into stable patterns of gene expression. Three important mechanisms involved in epigenetic regulations include DNA methylation, histone modifications and non-coding RNA (siRNA/ miRNAs) associated gene silencing. The interplay and progressive combination of these regulatory
mechanisms may “lock” the epigenome in specific states, thereby determining the fate and physiology of a given cell (Katada et al., 2012). Thus, intake of dietary methyl-groups (choline, methionine, genistein and folate) during critical periods of development can alter promoter DNA and histone (de) methylation/ (de) acetylation, resulting in life-long changes in gene expression and thereby altering the epigenome towards obesity in adulthood. Further, exposures to nutritional status (under-nutrition/over-nutrition) that occur at different developmental stages such as pre-conception, in utero and early life may result in epigenetic dysregulation, which put the individuals at a higher risk to develop chronic diseases later in life.

The methylome is the genomic distribution of methylated DNA sequence present in a cell and is capable of undergoing modification with respect to the environment/diet or the developmental stage (Kanherkar et al., 2014). DNA methylation occurs at the cytosine residues of DNA, especially in CpG dinucleotides present in regions called CpG islands. DNA methylation is generally associated with reduced transcriptional activity through decreased binding of transcription factors and also by attracting methyl CpG binding proteins that act as transcriptional repressors. Over 85% of CpG dinucleotides are spread out in the genome and located in repetitive sequences that are heavily hypermethylated/transcription - silenced in the normal cells, a state crucial to the integrity of the chromatin structure of the genome (Zhu and Yao, 2007). Further, genetic variation could have an effect on promoter DNA methylation percentages and subsequently on the regulation of gene expression (Kalashikam et al., 2014). On the other hand, histones are globular proteins around which DNA is packaged to make chromatin. Enzyme modifications, such as methylation and acetylation of lysine residues in their amino termini, lead to the conformational change in histones. Acetylation leads to increased DNA accessibility, and methylation can either increase or decrease DNA accessibility depending upon the specific type of methylation and histone modification (Yasui et al., 2003). DNA methylation and histone modification often work in tandem, as MBPs (methyl – CpG - binding proteins) recruited by DNA methylation that may exert their effects through recruitment of histone deacetylases, resulting in chromatin condensation and transcriptional inactivation.

Interplay of various regulatory mechanisms are expected to have regulatory roles in the inheritance and vulnerability to metabolic diseases i.e., obesity, type 2 diabetes, hypertension and CVD by affecting the expression(s) of the associated gene(s). Also, during specific developmental phases, intrauterine atmosphere can vary the epigenetics of an individual and may work as a foundation for the metabolic disease like obesity and other phenotypes during later stage of life. For example, variations in birth weight are affected by several factors like in utero and placental factors, maternal genes and BMI, paternal genes, smoking, alcohol consumption, drug use, and exercise during pregnancy etc. In a similar manner, poor/malnutrition during early and post-natal period also affects the mother’s metabolism to acclimatize and favour storage of nutrients in mother’s body. A study on Pima Indians showed that paternally imprinted gene located on chromosome 11 position 80 cM influences birth weight (Lindsay et al., 2002). Similarly, in a study on Mexican Americans, quantitative trait loci (QTL) on chromosome 6q, was found to be associated with birth weight regulation (Arya et al., 2006). Hence, gene-environment (GXE) interactions play a significant role in the aetiology of obesity, perhaps via modifications in DNA methylation patterns (Kalashikam et al., 2014). Apart from the well established fact that variations at DNA sequence level, the epigenetic incidents also seem to contribute to the development of metabolic diseases and its epidemiology, which is evident from modern day sedentary living style.

Research studies have shown that during the early years of life, monozygotic (MZ) twins are epigenetically indistinguishable from each other. Interestingly, with increasing age, remarkable differences become noticeable in their overall content and genomic distributions of 5-methylcytosine in DNA and histone acetylations. Similarly, diet/environment could have an influence on individual’s BMI and health. A comparative study of epigenetic metastability of 6,000 unique genomic regions between matched monozygotic (MZ) and dizygotic (DZ) twins demarcated epigenetic differences in both the MZ and DZ twins (Kaminsky et al., 2009). Molecular mechanisms of heritability may not be limited to differences in DNA sequence only. Indeed, epigenetic modifications also act as one of the very important governing factors in unravelling the secrets behind
the blue print of DNA sequence. Latest developments indicate that epigenetic research would add a new dimension by explaining inter-individual variations in body weight. With the use of advanced technologies, epigenetic profile of the metabolic diseases like obesity, CVD etc associated genes can be discerned and could be applied in a genome-wide approach. Latest technological developments and ongoing research on epigenetics aspects are continuously uncovering the role of epigenetics in a variety of human disorders and fatal diseases. The renewed interest in epigenetics has led to new findings about the relationship between epigenetic changes and a host of disorders including various cancers, mental retardation, immunity, neuropsychiatric and paediatrics. Specifically, it is very important to explore more about diet and epigenetic changes and its relation with development of metabolic diseases.

To understand the development and or progression of metabolic disease, the present day predictors are circumscribed by heritability, environmental factors such as diet, lifestyle, and gut microbiome. It is very clear that advances in nutrigenomics and epigenomics would further the understanding of the complex interplay between genotype, phenotype and environment, which are required for development of personalised nutrition in the future. Improving diet and other lifestyle behaviours’ has considerable potential for reducing the global burden of non-communicable diseases, especially metabolic diseases and promoting better health.

**Gene-nutrient Interaction**

Gene-nutrient interactions are complex and hard to predict, thus demonstrating the need for highly controlled genotypes and environmental conditions that allow identification of different regulatory patterns (Doo and Kim, 2015). Differences in genetic makeup or genotype are the factors that determine the phenotype; on the other hand nutrient imbalances could also play a key role (Nature Vs Nurture). Whether dietary intervention affect the outcome of phenotype (GXE=P) is determined by the diseased condition known to have genetic and/or environmental components (nutritional) (Perusse and Bouchard, 2000). A large number of studies have shown that nutrients alter gene expression at the level of gene regulation, signal transduction and through alterations in chromatin structure and protein function. All organisms in the universe, simple or complex, have the ability to respond to nutrient or nutrient/hormonal signals, which regulate gene expression i.e., synthesis of mRNA, encoding the enzymes involved in their metabolism (Qi and Cho, 2008). Nutrients such as macronutrients (fatty acids, proteins and carbohydrates) and micronutrients (minerals and vitamins) along with phytochemicals in food regulate/alter gene expression. Nutrients act as signalling molecules that activate cellular sensing mechanisms, which in turn degrade them (nutrients) into metabolites. Hence, the modifications in gene expression may affect muscle, liver, pancreatic β cells, hypothalamus, adipose tissue etc. The effects of these gene-nutrient interactions can be deleterious or protective thereby regulating energy homeostasis and metabolic pathways. Use of high throughput technologies has facilitated the collection of important information by studying the interaction of bioactive food components with genome at cellular and molecular level. Development of metabolic syndrome is practically linked with unbalanced nutrient intakes and generation of reactive oxygen (ROS) and nitrogen species (RNS). The nutrients keep the desired balance between total oxidation status and total antioxidant response of the organism to maintain a balance between these two variables (Rajoka et al., 2012).

**Metabolic Syndrome (Mets)**

The metabolic syndrome (MetS) is a clinical entity of substantial heterogeneity, represented by a cluster of biochemical and physiological abnormalities (Goyenechea et al., 2008; Phillips, 2013). The major risk factors for developing MetS are physical inactivity, diets rich in fats (particularly saturated fatty acids) and carbohydrates, contributing to the clinical features such as central obesity, insulin resistance, inflammation, hypertension and dyslipidaemia. Clustering of these risk factors leads to an increased risk for the development of type 2 diabetes and cardiovascular disease (Roche et al., 2005; Qing Song et al., 2006; Taylor et al., 2013; Han et al., 2016). Therefore, it is important to understand the biological impact of gene–nutrient-disease interactions that provide an insight into the pathogenesis and progression of metabolic syndrome.
**Obesity**

Obesity is an important clinical and public health challenge, characterized by excess adipose tissue accumulation resulting from an imbalance in energy intake and expenditure. It has become one of the major threats in the industrialized world not only among adults, but also among adolescents and children. It is influenced by the interaction of genes, nutrition, environment and lifestyle. Apart from environmental and social factors, genetic differences play an important role in the development of obesity (Rao et al., 2014). Central adiposity is the primary causal factor in developing insulin resistance, the hallmark of metabolic syndrome (MetS) (Roberts et al., 2013). Several studies have reported that mutations in a number of genes including leptin (LEP), leptin receptor (LEPR), pro-opiomelanocortin (POMC), fat mass and obesity- associated gene (FTO) and melanocortin-4 receptor (MC4R) are associated with fat accumulation and obesity development (Martínez et al., 2007; Fawcett et al., 2010; Deliard et al., 2013; Muller et al., 2014). Youssef et al. (2013) have reported that high energy intake is associated with the Trp 64 Arg polymorphism of ADRB3 gene, leading to significant increase in the risk of obesity. A promoter variant rs11872992 in MC4R has shown that increased food intake and decreased energy expenditure leads to increased risk for obesity. A mis-sense variant in the IL6R (interleukin 6 receptor) gene, Asp 358 Ala (T > G substitution) interacts significantly with dietary energy intake and the risk of abdominal obesity. Intake of total fat and saturated fatty acid (SFA) was significantly associated with waist circumference in individuals carrying the peroxisome proliferator-activated receptor alpha (PPARa) Leu 162/Leu 162 genotype, but not in those with the Val 162 allele (Youssef et al., 2013). A population-based study showed Gly 482 Ser of the PPARC1A gene was associated with increased risk of obesity only in elderly men (age ≥ 50) with low physical activity (Ridderstrale et al., 2006). Recently, a significant interaction between the FTO gene variant rs9939609 and physical activity in relation to obesity risk has been reported in a Danish population (Phillips, 2013). FTO gene was one of the first genes to be associated with BMI, with increased intake of nutrients and decreased satiety found to be more prevalent in subjects with MetS. Another study reported that a G>A transition at position -2549 in the promoter region of the LEP gene was shown to be associated with obesity and also the carriers of -2549A allele have higher leptin levels and lower weight loss despite they were subjected to low calorie intake (Basic et al., 2012). A clear understanding of potential gene-nutrient interactions, would give possible insights to manipulate diet in such a way to minimize the metabolic risk for obesity.

**Insulin resistance (IR) and impaired glucose tolerance (IGT)**

Impaired glucose tolerance (IGT) is a pre-diabetic state of hyperglycaemia that is associated with insulin resistance and increased risk of cardiovascular pathology (Nathan et al., 2007). Insulin is a pancreatic hormone that helps the body use glucose, the main source of energy which travels in bloodstream to cells throughout the body. As blood glucose level increases after a meal, the pancreas release insulin to clear excess glucose from circulation. Insulin resistance is a condition in which the body produces insulin but it is not used properly by metabolically active tissues such as muscle, adipose, and liver cells. As a result, their bodies need more insulin to help glucose enter the cells and over time this results in a condition called “hyperinsulinemia”. Subsequently, excess glucose builds up in the bloodstream, setting the stage for diabetes. Intervention studies have shown that high fat diets exacerbate insulin resistance and low-fat diets, have a beneficial effect (Zivkovic et al., 2007). Polymorphisms in adiponectin gene (APM1, ADIPOQ, ACRP30), and its receptors (ADIPOR1 and ADIPOR2) are strongly associated with obesity, type 2 diabetes and insulin resistance (Tschretter et al., 2003; Kitamoto et al., 2015). Further, studies reported that homozygosity of G allele rs3790433 for the leptin receptor (LEPR) was also associated with increased risk of insulin resistance and metabolic syndrome (Ferguson et al., 2010). Haplotype of the adiponectin gene is associated with several features of insulin resistance in non-diabetic individuals, including low serum adiponectin levels. In addition, associations of two single nucleotide polymorphisms (SNPs); the +276G>T (rs1501299), the +45T>G, (rs2241766) polymorphism in the adiponectin gene is associated with higher insulin levels and insulin resistance (Melistas et al., 2009). The presence of the risk allele for KCNQ1(Potassium Voltage-Gated Channel
Subfamily Q Member 1) variants rs2237897, rs2237892, and rs2283228 were found to be associated with increased fasting glucose level and decreased β-cell function (Tan et al., 2009). A non-synonymous variant of N-acetyltransferase 2 (NAT2) [rs1208 (803A>G, K268R)] is strongly associated with decreased insulin sensitivity that is independent of BMI (Knowles et al., 2015). One of the most studied polymorphism (rs1801253) in the ADRB1 gene codes for arginine or glycine at amino acid 389 (Arg389Gly) found to be associated with high levels of insulin and insulin resistance (Lima et al., 2007), and this allele is more prevalent in subjects with high body mass index (BMI). The intestinal fatty acid-binding protein (IFBP), coded by the FABP1 gene, is one of the most abundant proteins in enterocytes and its genetic variation was associated with insulin resistance in Pima Indians. Acetyl-CoA carboxylase β (ACC2) plays a key role in fatty acid synthesis and oxidation pathways, and studies showed that polymorphisms in ACC2 gene (rs2075263, rs2268387, rs2284685, rs2284689) were associated with impaired insulin sensitivity and metabolic syndrome (MetS) (Phillips et al., 2010).

**Dyslipidemia**

Dyslipidemia is one of the very early features of MetS and frequently precedes IGT. The pathological condition of dyslipidemia are associated with abnormal amount of lipids in circulation, particularly elevated levels of low density lipoprotein (LDLs) and decreased levels of high density lipoprotein (HDLs) (Bitzur et al., 2009). Dyslipidemia result in high levels of low-density lipoprotein (LDL), with more than 700 distinct mutations in LDL receptor genes. Increased triglycerides and decreased HDL cholesterol levels are mainly associated with mutations in the lipoprotein lipase (LPL) and apolipoprotein E (APOE) genes, which are important for lipoprotein metabolism. Several variants of the APOA1/C3/A4/A5 and APOE/C1/C2 gene clusters have been consistently associated with the characteristic dyslipidemia of the MetS. Apo E4, an iso-form of APOE, is very strongly associated with vascular inflammation and cardiovascular disease or increased risk for myocardial infarction (Phillips et al., 2008). Long-chain acyl CoA synthetase 1 (ACSL1) involved in mitochondrial beta-oxidation of long chain fatty acids and play an important role in fatty acid metabolism. Studies showed that polymorphisms in ACSL1 gene (rs4862417, rs6552828, rs13120078, rs9997745, and rs12503643) have been associated with insulin resistance and dyslipidemia (Phillips et al., 2010). A number of lipid sensitive transcription factors, including FXR, LXR, RXR, PPAR, PGC1alpha, PGC1 beta, SREBP-1a and SREBP-1c, have been implicated in the development of the MetS. PPAR is a good candidate gene for the MetS because of its multiple roles in adipocyte differentiation, fatty acid metabolism, insulin sensitivity and glucose homeostasis. The Pro12Ala polymorphism of PPAR has been identified as the most widely reproduced genetic variation for the risk of T2DM and an excellent example of the relevance of gene–nutrient interactions in the development of T2DM and MetS (Altschuler et al., 2000).

**Hypertension**

Hypertension or high blood pressure is a common disease worldwide. Arterial hypertension constitutes an important pathogenic element in obesity-associated metabolic syndrome, and CVD. Major risk factors for pathogenesis of hypertension include genetics, nutrients (sodium, chloride, low potassium and low calcium, low omega-3 fatty acid), obesity and other environmental factors (Rajoka et al., 2012). The genes responsible for renal water and electrolyte balance act directly by impacting the function of renal sodium transporters and indirectly by altering the expression of adrenal/mineralocorticoid hormones. Polymorphic genes implicated in blood pressure regulation include renin-angiotensin; including those encoding angiotensinogen (AGT), angiotensin converting enzyme (ACE) and aldosterone synthetase (CYP11B2). Angiotensin has two genotypes –AA and GG. On the same type of diet, individuals with AA genotype were found to have reduced blood pressure, but not individuals with GG genotype. Heterozygote AG genotype had intermediate level of blood pressure, but not individuals with GG genotype. Heterozygote AG genotype had intermediate level of blood pressure (Gard, 2010). Sodium transport/metabolism-related genes, such as those encoding for epithelial sodium channel (ENaC) subunits, 11B-hydroxysteroid dehydrogenase and adducin are of interest, given the well-proven association between dietary salt intake and hypertension. Recent genome-wide association studies (GWAS) have identified an association between blood pressure and the gene encoding for folate-metabolising enzyme, methylene tetrahydrofolate reductase (MTHFR) and showed an
increased risk of hypertension in people homozygous for the 677C–T polymorphism. Riboflavin in the form of FAD acts as a cofactor for MTHFR. CVD patients with the relevant MTHFR 677 TT genotype had significantly higher blood pressure as compared to CC or CT genotypes (McNulty et al., 2014). These patients were highly responsive to riboflavin intervention. Gene-based association scan found IGF1, SLC4A4, WWOX, and SFMBT1 associated with hypertension (Yang et al., 2012). IGF encodes insulin-like growth factor 1, which is associated with cardiovascular disorders, metabolic syndrome, decreased body weight/size and changes in insulin levels in mice. SLC4A4 (Solute Carrier Family 4 Member 4) encodes the electrogenic sodium bicarbonate co-transporter 1 and is associated with decreased body weight/size and abnormal ion homeostasis in mice. Similarly, WWOX encodes the WW domain-containing protein, which is related to hypoglycaemia and hyperphosphataemia. SFMBT1, which encodes the Scm-like with four MBT domains protein 1, is a novel hypertension gene.

**Inflammation**

Diet is an important regulatory factor in immune response; while malnutrition leads to susceptibility to infections due to immuno-suppression, over-nutrition leads to immuno-activation due to susceptibility to inflammatory condition. Therefore, optimal nutrition is required for a healthy immune balance. Observational and interventional studies suggest that diets rich in trans fats and/or saturated FAs are highly related to the immune response by increasing the circulating pro-inflammatory cytokines; interleukin-6 (IL-6), C-reactive protein (CRP), tumour necrosis factor- alpha (TNF-α) (Hansongyi et al., 2013). Therefore, high fat and/or carbohydrate diet causes excessive body fat accumulation, impairs immune system and affects the inflammatory status. Obesity (a crude index of adiposity/BMI) is associated with alterations in immunity (a chronic low-grade inflammation) in which there is an elevation of a variety of circulating adipokines, including leptin, adiponectin, resistin, and visfatin, as well as pro-inflammatory cytokines such as IL-6, CRP, interferon gamma (IFN-γ), and TNF-α etc (Shoelson et al., 2007; Hansongyi et al., 2013). These elevated pro-inflammatory molecules produced by the adipose tissue are implicated as active participants in the development of metabolic syndrome (Nino-Fong et al., 2007). Adipose tissue not only acts as major energy storage tissue but is also a metabolically dynamic endocrine organ and an important source of several bioactive compounds such as hormones, cytokines, chemokines, growth factors and complement proteins. These substances play a central role in the whole body homeostasis by influencing a variety of biological and physiological processes such as food intake, energy balance, insulin action, glucose/lipid metabolism, angiogenesis/vascular remodelling, blood pressure, and coagulation. Excessive fat storage in adipose tissue due to positive energy balance (excess nutrient intake) leads to hypoxia and hypoxia-induced fibrosis, adipose tissue cell death, and adipocyte stress, which in turn trigger the chronic systemic low grade inflammation. Studies have shown that TNF-α-308G>A polymorphism in the promoter region is associated with increased plasma TNF-a concentrations and is associated with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome (Hoffstedt et al., 2000; Vendrell et al., 2003; Gupta et al., 2012). The association between -174G>C polymorphism (rs1800795) in the promoter region of the IL-6 gene and insulin resistance is modified by body mass index (BMI) (Underwood et al., 2012). A study showed that the concomitant presence of promoter polymorphisms of TNF-a (G-308A) and IL-6 (C-124G) in obese subjects with impaired glucose tolerance carry twice the risk of conversion to type 2 diabetes, when compared with other genotypes (Kubaszk et al., 2003).

**Consequential Risks Associated With Metabolic Syndrome**

**Type 2 Diabetes (T2DM)**

Type 2 Diabetes Mellitus characterized by hyperglycaemia, results from defects in insulin secretion and activity or both. It is associated with dysfunction and failure of different organs, such as blood vessels, heart and kidneys. T2DM is clinically defined as having an overnight fasting serum glucose ≥ 126 mg/dL or a haemoglobin A1c (HbA1c) > 6.5%. Diabetes is more prevalent among specific ethnic/racial groups, providing evidence for genetic predisposition. Genetic and functional data indicate that CAPN10 (which encodes cysteine protease calpain 10) plays an important role in insulin resistance
and intermediate phenotypes. Calpain 10 (CAPN10) was the first T2DM susceptibility gene identified through a genome-wide scan followed by positional cloning (Dedoussis et al., 2007). CAPN10 variants have been linked with several MetS phenotypes, including hyper triglyceridemia, BMI and hypertension. Studies have reported that six genes account for majority of the monogenic forms of diabetes. These are hepatic nuclear factors (HNF-1α, 4α and 13), glucokinase (GCK), insulin promoter factor-1 (IPF-1), and neuro D1 transcription factor (NEUROD1) (Gloy, 2003). Further, Transcription factor 7–like 2 (TCF7L2) gene variants (rs7903146 SNP) are specially associated with an increased risk for T2DM and MetS by causing excess fat and glycogen deposition in the liver, glucose intolerance and hyperlipidaemia (Phillips, 2013). A study reported that the gene, Two pore segment channel 2 (TPCN2) plays a role in metabolic regulation, and the single nucleotide polymorphism rs1551305 in TPCN2 is associated with type 2 diabetes risk (Fan et al., 2016).

The KCNJ11 gene, a member of the potassium channel gene and the common polymorphisms (SNPs) in KCNJ11 gene, such as rs5219, rs5215, rs5210, rs5218, rs886288, and rs2285676 were shown to be involved in diabetes (Haghvirdizadeh, 2015). A study reported that KCNJ11 SNPs 74 (3p+215), 76 (A190) and 77 (E23K) showed significant association with T2DM (Dedoussis et al., 2007). FABP (FABP1) is an abundant cytosolic lipid-binding protein that regulates lipid transport and metabolism. The c.334-135G>A polymorphism (rs2197076) located in the 3 prime un-translated region (UTR) of the FABP1 gene was associated with the risk of type 2 diabetes and the homeostatic model assessment index (HOMA index) (Mansego et al., 2012).

Several studies in humans and animal models have shown anti-diabetic effects of dietary flavonoids on glucose homeostasis by regulating expression of different genes in pancreas, liver, skeletal muscle and white adipose that are involved in various cellular pathways. Consumption of anthocyanins, particularly from blueberries, apples and pears, was consistently associated with a lower risk of T2DM (Berna et al., 2014). These compounds were shown to regulate carbohydrate digestion, insulin secretion, insulin signalling and glucose uptake in insulin-sensitive tissues by modulating intracellular pathways. Naringin and hesperidin, the two major flavanones present in citrus fruits have also been shown to protect against T2DM by activating peroxisome proliferator activated receptors (PPARs) in liver and adipose tissue. Studies in mice showed that bilberry anthocyanin supplementation improved insulin sensitivity in T2DM by down regulating the expression of gluconeogenic enzymes and up regulation of peroxisome proliferator activated receptor alpha (PPARα), long chain carnitine palmitoyltransferase 1 (L-Cpt-1), Glucose transporter type 4 (Glut4) and aconitase (Aco) expression in the liver (Takikawa et al., 2010). The dietary flavones, apigenin and luteolin found in celery, parsley were shown to protect the cells from cytokine-induced apoptosis by inhibiting inducible nitric oxide synthase (iNos) expression. The major dietary isoflavones; daidzein and genistein, primarily present in soy foods have been shown to improve glucose tolerance and circulating insulin concentration by increasing islet α cell proliferation, β cell mass and survival (Kim et al., 2007). The genotype and diet interaction studies showed that peroxisome proliferator-activated receptor gamma (PPARG) Pro12Ala genotype modified the association between total dietary fat intake and risk for obesity. The Pro/Pro homozygotes of PPARG have been reported to be at increased risk for obesity and insulin resistance (Roche et al., 2005). Scavenger Receptor Class B Member 1(SCARB1) genetic variability plays a significant role in lipoprotein metabolism. Research findings show that subjects carrying the A allele in exon 1 at the SCARB1 gene locus (SCARB1 exon 1, rs4238001) were associated with significant increase in insulin sensitivity after the consumption of a MUFA-rich diet compared to the effect on G/G individuals (Dedoussis et al., 2007). The fatty acid (FA)-binding protein 2 (FABP2) gene that codes for intestinal FABP (IFABP), is crucial for fat absorption and transport. Subjects with the Thr54 allele had higher FA concentrations than did those who were homozygous for the Ala54 allele when consuming a saturated fatty acid (SFA)-rich diet. This suggests a plausible mechanism for the FABP2 Ala54/Thr54 polymorphism-diet interaction for the determination of insulin sensitivity and T2D (Dedoussis et al., 2007).

**Cardiovascular Disease (CVD)**

CVD can be characterized as a group of multifactorial conditions that include cerebro vascular diseases (stroke with transitory ischemic attack),

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peripheral vasculopathy and cardiac ischemic disease (CHD), which includes acute myocardial infarction (AMI), angina pectoris and sudden death (Jannes et al., 2004). The major risk factors associated with cardiovascular diseases are age, family history, sedentary lifestyle, physical inactivity, hypertension, obesity, diabetes and high blood cholesterol. All these pathological entities are closely related to both genetic factors and environmental influences (Rajoka et al., 2012). CVD may also result from a variety of genetic causes, including single-gene mutations, interaction of multiple genes and environmental factors.

Obesity per se is a major cardiovascular risk factor and polymorphic genes involved in controlling energy balance provide “favourable” or “unfavourable” background for the development of CVD. Elevated plasma levels of total cholesterol, LDL cholesterol and triglycerides predispose to the development of atherosclerotic plaques. Apolipoprotein (apo) A-1 is a key component of HDL and both apo A-1 and HDL cholesterol have been identified as protective factors for CVD. Genetic variation in genes encoding apolipoproteins, some enzymes and hormones can alter individual’s sensitivity to develop the CVD (Ordovas, 2006). Individuals with the E4 allele in the apolipoprotein E gene show higher low-density lipoprotein (LDL)-cholesterol (bad cholesterol) levels with increased dietary fat intake compared with those with the other (E1, E2 and E3) alleles receiving equivalent amounts of dietary fat. Polymorphism in genes encoding lipid transport proteins, their receptors, and lipid-processing enzymes and inflammation-related proteins are associated with the characteristic changes in blood lipid concentrations.

Conclusion

Since ancient times, humans have known that environment and food can interfere with an individual’s health/disease condition, and have indeed used food and plants as medicines. Human genome has provided and increased the information on the genetic order of polymorphic markers and the SNP map of the humans. This provides powerful molecular tools to decipher the role of nutrition in human health and disease and help in defining optimal diets. Advanced genetic analysis may provide opportunities to understand the basis of complex traits and the role of individual genotypes on the development of polygenic diet-related diseases such as CVD and T2DM. Adequate dietary nutrients not only prevent or delay chronic disorders, but also decrease the progression and severity of chronic diseases. The challenge for nutrigenomics researcher is to discover the genes, their associations to diets (Gene X diet interaction) and development of chronic diseases (gene-diet-disease interaction). Trials should be designed effectively taking into consideration, the ‘ethics’ as well the ‘ways of implementing research and science into the need of the society’. Therefore, the use of individual genetic information, avoiding obesogens (foreign chemical compounds that disrupt normal development and balance of lipid metabolism, which in some cases, can lead to obesity) and a healthy lifestyle could help to improve the management of metabolic syndrome. The knowledge of genetics and epigenetics reinforces the importance of nutrition in health and disease. It is very clear that advances in nutrigenomics and epigenomics would undoubtedly further the understanding of the complex interplay between genotype, phenotype and environment, which are required to enhance the development of personalised nutrition in the future.


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