REVIEW ARTICLE

Epigenetic in DNA Methylation and Metabolic Syndrome

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ABSTRACT

Prevalence of metabolic syndrome varies depending on ethnicity and gender, indicating that it is associated with genetic factors. The occurrence of this disease is influenced not only by gene variations but also by gene promoters that can be activated or deactivated by environmental factors through epigenetic mechanisms. Epigenetics involves environmental factors that influence specific cells through DNA changes that modify gene expression in promoters. Through this mechanism, DNA methylation can alter metabolism and lead to the development metabolic diseases. Certain dietary components and physical activity can increase DNA methylation or demethylation in gene promoters, which affect the risk of disease or inhibit the disease. Understanding environmental risks for the development of metabolic syndrome through DNA methylation and demethylation is crucial for the therapy, diagnosis and prognosis of this disease through the selection of appropriate nutrition

Keywords: Diet, DNA Methylation, Epigenetic, Histone, Metabolic Syndrome

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INTRODUCTION

Metabolic syndrome is a group of metabolic disorders (e.g., abdominal obesity, glucose intolerance, insulin resistance (IR), high blood pressure, and dyslipidemia) that increase the risk of chronic diseases, such as cardiovascular disease, type II diabetes mellitus (T2DM), and some types of cancer. A recent study by the Centers for Disease Control has reported that the incidence and frequency of metabolic syndrome varies depending on ethnicity and gender, indicating that it is associated with genetic factors. Epigenetics involves environmental factors that influence specific cells by chemical changes in DNA that modify gene expression (1).

Methylation of DNA occurs at the site of cytosine nucleotides followed by guanine nucleotides (CpG) and produces 5-methylcytocin, which affects gene expression. Sites of CpG are located in the promoter of gene. Certain gene promoters are easily hypomethylated in the presence of an environment or diet, whereas other areas of DNA are easily hypermethylated (2). Transcriptional repression is correlated with hypermethylation and activation of gene is associated with hypomethylation (3). Alterations in candidate gene methylation are associated with excess body weight with dietary control and metabolism, insulin action, lipid catabolism and anabolism, immunity, inflammation, growth, high blood pressure, and regulation of the circadian clock (4). The leptin (LEP), neuropeptide Y (NPY) and pro-opiomelanocortin (POMC) genes, which participate in maintaining of body weight, have CpG islands, where methylation and demethylation can affect the expression or supression of these genes. Some obesity-associated genes, including adiponectin (ADIPOQ), peroxisome proliferator-activated receptor coactivator 1 (PGC1α), insulin-like growth factor 2 (IGF2), insulin receptor substrate 1 (IRS1), and lymphocyte antigen, are associated with DNA hypermethylation and T2DM. Meanwhile, lipoprotein lipase (LPL), adrenergic receptor B3 (ADRB3), ATP-binding Cassette G1 (ABCG1), tumor necrosis factor (TNF)-α, methylene tetrahydrofolate reductase (MTHFR), and some other methylation of these genes are correlated with lipid metabolism, IR, and hypertension. Post-translational of the histone core modification, including acetylation, methylation, ubiquitination, phosphorylation, and histone tail sumoylation, is an important mechanism in epigenetic regulation. Acetylation of histone is associated with gene transcription. Histone deacetylation can cause interactions between DNA and histone structure, causes compression of and influence lowering of transcription (5). DNA methylation and histone modification are interrelated. DNA methylation influence modification of histone, and vice versa, by affecting chromatin in RNA polymerase and transcription factors (6).

The epigenetic reaction becomes sensitive to environments and nutritional factors during

developmental transition, the period when epigenetic markers are critically modified. Thus, nutritional deficiencies during pregnancy and lactation have long-term consequences in health. Studies in the Netherlands and Gambia provided examples of nutritional deficiencies leading to dysregulation in metabolism in later life, which have been linked to cardiovascular disease, excess of body weight, or high of glucose in the blood (7).

Macronutrients (polysaccharides, proteins, and lipids) and micronutrients (vitamins, minerals, and some bioactive components) alter the repressor and/or activator complexes at the promoter gene, modulating gene expression/repression. Intake of nutrition and habits of diet influence the predisposition of certain diseases due to this epigenetic mechanism (8). Malnutrition caused by over nutrition also induces epigenetic changes in gene promoters in the metabolic pathway, which can influence gene expression and metabolic changes. High-fat diets with saturated and trans-fatty acids induce promoter hyper methylation, which is associated with impaired intestinal permeability, obesity, cardiovascular disorders, impaired insulin secretion, and increased T2DM risk (9).

Exercise is an environmental factor that influences DNA methylation and the risk of metabolic syndrome disease. Research related to exercise shows that DNA methylation of genes in metabolism of vitamin A (retinol), signaling pathways calcium mineral, and those associated with T2DM decreases after exercise. Changes of methylation caused by exercise correlated with differential gene expression (10). Exercise induces genome-wide changes in DNA methylation in human adipose tissue, influencing adipocyte metabolism and in some genes correlated with lining endothelium influencing cardiovascular system.

This review discusses that methylation on promoter DNA can cause metabolic syndrome, which is composed of obesity, insulin resistance, dyslipidemia, and high blood pressure, and that diet affects DNA methylation that modifies gene expression.

The incidence of metabolic syndrome is increasing rapidly in many countries, affecting 20% of the adult population in the world. In 2010, 38.37% of Spanish people and 29.62% of women showed indications of metabolic syndrome, and this trend has increased with age (7).

Human studies analyzed the relationship between m e t h y l a t e d i n DNA and metabolic syndrome in visceral adipose tissue, insulin sensitivity, high blood pressure, low HDL-C lipoprotein level, and high triacylglycerol in the blood. A genome-wide association study (GWAS) with 8165 participants found associations between adipose and changes in DNA methylation in blood cells and adipose tissue. These data relate to changes in DNA methylation, mediated by visceral adiposity (11). Another study with 64 subjects found a correlation between methylation in the promoter genes of lipoprotein lipase in individual hypertriglyceridemia and the development of metabolic syndrome (12). Another GWAS study with 483 children identified differentially methylated regions (DMRs) that are associated with insulin sensitivity (13). Some genes are also involved in the dysregulation of carbohydrate metabolism, hyper-triacylglycerol, and decreased leves of HDL-C, which participate in the development of insulin sensitivity and cardiovascular disease (14,15). Other studies found a correlation between the methylation of genes that cause changes in blood pressure and vascular endothelial function, which are associated with hypertriglyceridemia (7).

DNA METHYLATION AND OBESITY

The prevalence of obesity has increased since 2016, with nearly 2 billion adults with excess of weight and 650 million obese (16). Obesity is defined as the excess fat that contributes to the development of comorbid diseases, such as cardiovascular disease, dyslipidemia, high blood pressure, T2DM, and metabolic syndrome (17). Obesity is associated with an energy imbalance between input and expenditure calories. This balance is influenced by several factors, such as lifestyle (diet, exercise, and sleep patterns), economic factors (level of education and economic status), endocrine disease (hypothyroidism, growth hormones), or medications (corticosteroid administration). In addition to environmental factors, genetic factors also influence the development of obesity (7,18).

Hypertrophy and hyperplasia of adipocyte cells in obesity reduce oxygen availability and cause hypoxic stress, which is associated with inflammation, insulin resistance (IR), and mitochondrial dysfunction. Hypoxic conditions increase reactive oxygen species (ROS) generation and oxidative stress as mediators of inflammation (19). Obesity is almost always associated with IR, and poor glycemic control is associated with epigenetic changes involved in the development of diabetes-related comorbidities. Pathomechanism of obesity with component of metabolic syndrome are some genes, such as POMC(20), NPY(21), SREBF1 (21), leptin (22), Hypoxia-induced Factor IIIA (HIF3A)(23) melanocortin, (24), insulin-like growth factor binding protein 3 (IGF3), TNFα (25), and clock circadian regulator (26), are affected by epigenetic because of environmental factors causes change in methylation or demethylation of DNA that influence the expression of gene. Glycolysis-related HIF system control genes, such as pyruvate dehydrogenase kinase-1 (PDK-1), lactate dehydrogenase-A (LDH-A), and glycogen phosphorylase, stimulate glucose uptake or increase glucose synthesis by activating PEP-carboxykinase in the liver (27).

Some GWASs identified more than 500 locus genes that affect obesity incidence. Genetic, environmental, and lifestyle factors can affect DNA methylation and contribute to the pathogenesis of obesity. Research on the DNA methylation of peripheral blood leukocytes found CpG sites in people with obesity (28). Variations in DNA methylation occur in subjects with obesity compared to those normal weight, and methylation differences could predict obesity to reach 70%. Research on white blood identified five CpG sites in HIF3A and found that increased levels of methylation are correlated with increased body mass index (BMI) (Figure 1).

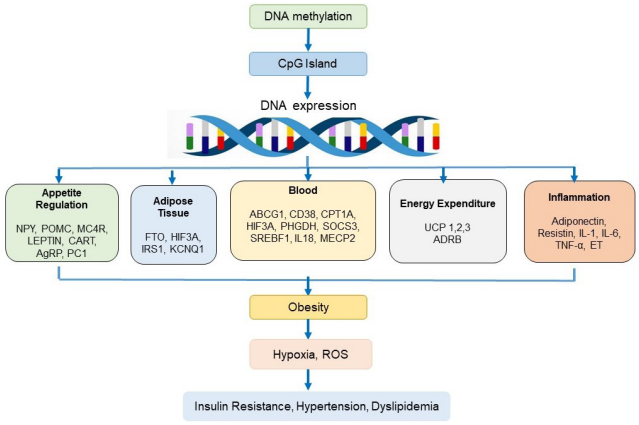

Figure 1: Correlation of obesity genes and DNA methylation influences metabolic syndrome. (Abbreviation: *ABCG1= ATP binding Cassette sub family G1, ADRB= Adrenergic Receptor Beta, AgRP= Agouti –related Protein, CART= cocaine- and amphetamine-regulated transcript , CD38-Cluster of Differentiation 38, CPT1A= carnitine palmoyltransferase 1A , ET= Endothelin, FTO= fat mass and obesity-associated , HIF3A= Hypoxia-inducible Factor 3A, IL= Interleukin, IL18= Interleukin-18, IRS = insulin receptor ,ubstrate, KCNQ = Kalium voltage-gated channel subfamily Q, MC4R= melanocortin-4 receptor, MCEP2= methyl-CpG binding protein, NPY= Neuropeptide Y,PC1- Pro-convertase-1, PHGDH = phosphoglycerate dehydrogenase, POMC= ProOpiomelanocortin, SOCS3=Supressor of Cytokine Signaling-3, SREBF1= sterol regulatory element binding transcription factor 1,TNFα= tumor necrosis factor α, UCP= Uncoupling Protein*)

Other studies investigated CD4+T cells and identified eight CpG sites are associated with BMI and waist circumference and waist/hip ratio. These include four CpG sites on Carnitine palmitoyl transferase (CPT1A), CD38, and Phosphoglycerate dehydrogenase (PHGDH). CPT1A encodes the carnitine palmoyltransferase 1A enzyme that plays a role in the transport of carnitine-dependent lipids through mitochondrial membranes to carry long-chain fatty acids into the mitochondria. CD38 is associated with metabolic diseases, and research with mice lacking CD38 showed a rapid metabolic rate and resistance to obesity during the administration of a high-fat diet. In patients with obesity, proteins encoded by ATP binding cassette sub family G1 (ABCG1) are associated with macrophage cholesterol and phospholipid transport (29).

Another research found that 87 CpG sites associated with BMI affect changes in the ABCG1, SREBF1(30), and CPT1A genes, which play a role in fat metabolism pathways (31). SREBF1 encodes transcription factors that participate in lipid anabolism and catabolism and serve as a target for the prevention of arterial coronary disease. The increase in the number of CpG sites is significantly related to body weight and waist circumference. Other studies on Musashi binding protein 2 (MS12) and Leucyl- tRNA syntethase-2 (LARS2) have been related to the expression of ABCG1, SREBF1, and CPT1A. MSI2 encodes the Musashi RNA binding protein 2 gene, which influences the post-translational regulation of genes related to eating habits (32). Other studies found a correlation among methylation of DNA, gene expression, and obesity in the SOCS3 gene, where obesity is associated with decreased methylation and increased gene expression. Expression of SOCS3 is upregulated in individuals with obesity and induces insulin and leptin resistance, which increase glucose level and disturb energy homeostasis (33). Interactions between stress and methylation of DNA at CpG site in SOCS3 are associated with BMI (34).

Methylation of DNA and obesity are related to adipose tissue, appetite regulation, hormones, energy expenditure that causes inflammation. Thousands of CpG sites on the subcutaneous adipose tissues are associated with BMI. In addition, 2825 genes successfully identified from methylated DNA and gene expressions are associated with BMI; these genes include FTO, Leptin, UCP2, and IRS1. A previous study with female subjects reported three CpG HIF3A sites that are significantly associated with BMI, whereas a research on male subjects found only 1 HIF3A Cp site that is significantly associated with BMI. In subcutaneous adipose tissue, CpG KCNQ1 sites involve low methylated DNA, which is also related to obesity. DNA-methyltransferase (DNMT3A and 3L) shows decreased methylation due to weight loss, as observed in Methyl-CpG-binding domain protein 4 (MBD4), the gene that encodes proteins and is specifically bound to methylated cytosine that influence signal methylation . Studies involving subjects who underwent gastric by-pass surgery found 8504 CpG sites, of which 27% are associated with adipogenesis (35). Methylation of CpG 147,161 sites occurs in the differentiation phase from myoblast to myotube in individuals with obesity. This phenomenon is due to genetic changes found in ENHO, IL18, MECP2 and PLCB1, which are involved in immune response, explaining how obesity can interfere myogenesis and affect muscle regeneration and function (36) (Figure 1).

DNA METHYLATION AND DIABETES MELLITUS

Diabetes mellitus is a common condition worldwide. More than 500 million people have T2DM, with a global prevalence of 8.5% in adults. High blood glucose caused 3.7 million deaths in 2012 alone (37). T2DM, with the highest frequency in all DM diseases, is characterized by decreased insulin production or high insulin concentration but receptor does not respons to insulin action (IR). Genetic and environmental factors

influencing T2DM risk include age, gender, ethnicity, smoking, obesity, poor physical activity, family history, gestational diabetes mellitus history, and some treatments, and these factors can be associated with nutrigenomic and epigenetic modifications (38). Methylated DNA in the pancreas, adipose tissue, skeletal muscle, and liver tissue changes during T2DM pathogenesis (39). Studies on epigenetic conditions have been conducted on several T2DM-related organs, such as the pancreas gland, skeletal muscle, adipose tissue, and liver tissue. Results from a number of human epigenetic studies on T2DM disease are shown in Figure 2.

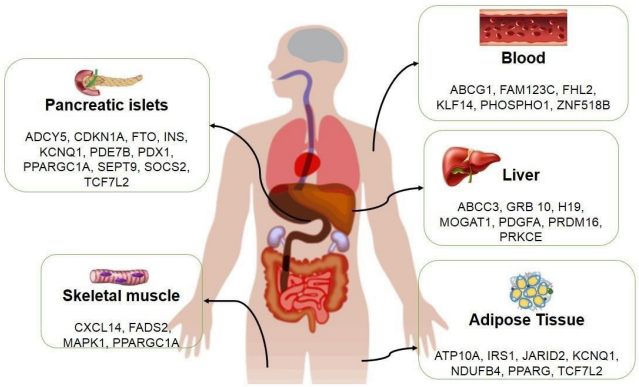

Figure 2: Epigenetics of gene in organs causes Type 2 diabetes mellitus. (Abbreviation: *ABCC3 = ATP binding Cassette sub family C2, ABCG1= ATP binding Cassette sub family G1, ADCY5= Adenylil Cyclase-5, ATP10A= ATPase Phospholipid Transporting 10A, CDKN1A= Cyclin- Dependent Kinase Inhibitor 1A, CXCL14= C-X-C motif chemokine ligand 12, FADS=fatty acyl desaturase, FAM123= Family gene of tumor supressor, FHL= familial hemophagocytic lymphohistiocytosis, FTO= fat mass and obesity-associated, INS= Insulin, GRB10= Growth factor receptor-bound protein-10, H19= Histone deacetylase, IRS1 = insulin receptor substrate-1, JARID2= Jumonji And AT-Rich Interaction Domain Containing 2, KCNQ = Kalium voltage-gated channel subfamily Q, KCNQ1=Kalium voltage-gated channel subfamily Q member 1, KLF = Kruppel Like factor, MAPK= mitogen-activated protein kinase, MOGAT1= monoacylglycerol O-acyltransferase 1, NDUFB4= NADH dehydrogenase (ubiquinone) family B4, PDE7=Phosphodiseterase, PDGFA platelet-derived growth factor A family, PDX1= Pancreatic duodenal homeobox 1, PPARG= peroxisome proliferator-activated receptor gamma, PRDM= Positive regulatory domain, SEPT = Septin, SOCS= suppressor of cytokine signaling, TCF7L2= Transcription factor 7 like 2, ZNF518B=Zink Finger Protein 518B*)

Methylation of the Ins2 promoter influences protein binding, which inhibits the activation of the insulin-synthesizing gene (40). On T2DM, the expression of GLUT4 is decreased in adipose tissue (41). Experiments in animals have shown increased phosphorylation of tyrosine or serine in IRS1 due to the hyperactivity of c-Jun N- terminal kinase, and endoplasmic reticulum X-box binding protein-1 causes decrease of insulin sensitivity (42). Excess free fatty acids due to lipolysis from triglyceride are stored in adipose tissue under the mediation of hormone-sensitive LPL, will release fatty acid and these fatty acids contribute to the occurrence of IR because of impaired insulin secretion pathway. High-fat accumulation causes monocyte infiltration, whichtriggers the release of proinflammatory cytokines. This phenomenon further inhibits insulin antilipolytic activity and ultimately causes increased insulin resistance. Peroxisome proliferator-activated receptor gamma (PPARγ) is a nuclear hormone receptor that targets many genes involved in inflammation and insulin sensitivity (43).

Mechanism of DNA methylation, including pancreatic and duodenal homeobox 1 as insulin promoter factor-1 (44), PPARG-Coactivator 1-Alpha (45), and GLP1Receptor (4 6) in the pancreas glands of patients with T2DM; increased methylation of DNA inhibit expression of these genes are associated with impaired insulin secretion as pathogenesis of T2DM. High levels of monosaccharide as glucose and hemoglobin as glycated (HbA1c) can directly increase DNA methylation in this gene (47). DNA methylation that influence the expression of CDKN1A, PDE7B, and SEPT9, causes increased gene expression in the pancreas (Figure 2). Research on CDKN1A and PDE7B genes showed that the promoter methylation during transcription causes overexpression of the protein inhibit insulin secretion. Overexpression of CDKN1A that encodes cyclic- dependent kinase inhibitors and regulates cell cycles toward G1 can decrease cell proliferation. DNA methylation also occurs in CpG sites of several T2D and obesity gene candidates, such as ADCY5, FTO, KCNQ1 (48). These gene methylation causes inhibit expression of gene and influence the metabolism correlated these gene.

Previous research used Illumina arrays to compare T2DM and controls that analyze methylation of DNA in skeletal muscle , adipose tissue and liver tissue (49). The results identified a number of CpG sites with DNA methylation changes in the target tissue of patients with T2DM, which support epigenetic patterns. Another study used sequencing to analyze 83% CpG site in human genome on the pancreatic glands of patients with T2DM and controls (50). This analysis identified m o r e t h a n 25 thousand DMRs in the pancreatic gland of patients with T2DM. Significant DMRs are present in PDX1, which is an importance role in transcription factor that regulate insulin expression in gland. About 159 other DMRs related to T2DM are in ADCY5, TCF7L2, and KCNQ1. In addition, some genes, including NR4A3, PARK2, PID1, and SOCS2, occur in DMRs and correlate with changes in expression in the pancreatic glands of patients with T2DM. When the candidate gene is overexpressed or silenced in beta cell culture, insulin secretion disorders occur correlated with epigenetic mechanisms to islet cell dysfunction (51). Methylation level in the pancreatic islet is associated with the disruption of histones and affects the control of gene activity and chromatin structure. A previous study used methylated DNA immunoprecipitation-seq to analyze the blood of monozygotic twin pairs and found strong replication signals in MALT1, which encodes insulin proteins and glycemic pathways and is correlated with taurocholic levels in the blood (35).

Genetic changes by diet and environment or epigenetic in patients with diabetes contribute to vascular complications. In addition, modification by epigenetic can result in complications of diabetes and some other diseases caused by vascular impairment are stroke, and myocardial infarction (52,53).

DNA METHYLATION AND HYPERTENSION

High blood pressure that are high sistolic and or diastolic blood pressure is a global health challenge and a major risk of cardiovascular disease, especially stroke and heart disease. Genetic variation contributes to the risk of high blood pressure with the variability of genetic factors between 30%–70% that affect blood pressure (46). Systemic high blood pressure is a condition of high blood pressure in systemic arteries with a blood pressure more than 140/90 mm Hg in adults. A recent report in 2017 from the American College of Cardiology/ American Heart Association (ACC/AHA) updated guidelines that modified the classification of high blood pressure more than 130/80 mm Hg (54). High blood pressure is a risk factor for heart disease such as myocardial infarction, heart failure, kidney disease such as end-stage kidney, and vascular disease such as stroke. According to the ACC/AHA report, men have a higher risk of developing hypertension than women in pre- menopausal age, indicating that hormonal signaling participates in the regulation of blood pressure. Chronic conditions that increase the risk of high blood pressure include age, smoking, low socioeconomic and educational conditions, overweight/obesity, diet high fat and glucose, sedentary life, and other secondary disorders, such as chronic kidney disease, family genetic history, diabetes mellitus, and stress conditions. Many signaling pathways correlated with the development of hypertension, such as molecular mechanisms, are associated with epigenomic regulation. This regulation relates to genotypes and phenotypes that are important for normal function and can affect the cellular function of tissues or organs in disease development. Epigenetic regulations that have been identified in hypertension include methylated, acetylated, phosphorylated, ubiquitinated, and sumoylated reaction in CpG site (55).

Methylation of DNA in DNA repetitive elements, such as ALU element and Long Interspersed Element-1 (LINE-1), is a genomic methylation that occurs up to 50%. Methylation events occur consistently in LINE-1 and ALU. Demethylation occurs consistently in LINE-1 and ALU. A recent study of the LINE-1 gene has found that decreased methylation levels affect high systole hypertension and diastolic blood pressure. DNA hypermethylation in LINE-1 is related to inflammatory responses due to endothelial damage and causes increased deaths because of chronic kidney disease (56).

Several studies focused on hypertension or cardiovascular disease-related genes, such as ADRB3, ABCG1, GALNT2, and HMGCR. Other studies analyzed proinflammatory genes and biomarkers, such as IFN γ, F3, GCR, ICAM-1, TLR-4, NFKB1, PPARγ, and IL-6, or other genes involved in inflammation responses, such as IL6, TNF-alpha, renin–angiotensin–aldosterone system (RAAS), a hormonal system that regulates physiological responses of hypertension (57). RAAS genes include promoter angiotensin I- converting enzyme (ACE) and angiotensin II receptor type I (55). The RAAS system, ADH and natriuretic peptide plays an important role in fluid retention that maintains blood pressure and is involved in high blood pressure pathogenesis (Figure 3) (58).

There are some kinds of receptor of Angiotensin include type-1 (AT1) and type-2 (AT2), which are G-class protein receptors with angiotensin as their ligand. AT1 receptors consist of the AT1a and AT1b subunits. High of AT1 receptors activation leads to the development of high blood pressure disease through its effect on angiotensin II in renal blood vessels. A previous research showed greater expression of AT1a mRNA and protein in mice that cause hypertension spontaneously compared with control mice. This hypertensive response is related to the hypomethylation in AT1aR promoters. ACE is a key enzyme in RAAS that helps regulate blood pressure. The identification of two CpG islands in the proximal promoter region of the ACE-1 gene affects the ACE expression modulated by CpG methylation and inhibition of histone deacetylation. Methylated promoters in ACE may play an important role in the expression of ACE-1 and the development of high blood pressure (59).

RAAS is correlated with the endothelium system, especially endothelin converting enzyme1 (ECE-1), a key enzyme in endothelin biosynthesis and is mainly

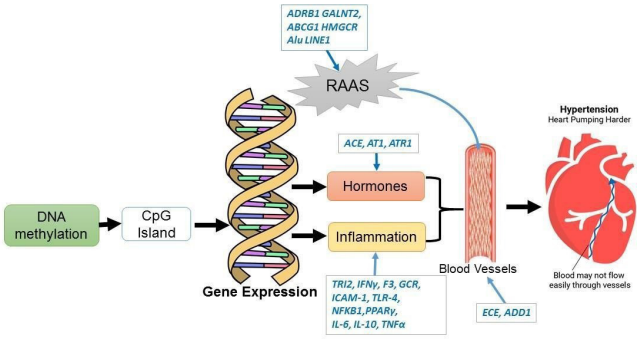

Figure 3: Methylation of DNA causes hypertension through the R enin–Angiotensin–Aldosterone System, Hormones and inflammation cause impaired blood vessels. (Abbreviation: *ABCG1= ATP binding Cassette sub family G1, ACE= Angiotensin Converting Enzyme, ADD1= Adducin-1, ADRB= Adrenergic Receptor Beta, AT= Angiotensin, ATR= Angiotensi n receptor, ECE= Endothelin converting enzyme, F3= Coagulation Factor III, GALNT2= N-Acetyl-Galactosaminyl Transferase 2, GCR= Glucocorticoid Receptor, HMG-CR, 3-Hydroxy-3-Methylglutaryl-CoA Reductase ICAM1= Intracellular Adhesion Molecule -1, IFNγ= Interferon γ, IL10= Interleukin-10, IL6= Interleukin-6, line1= Long Interspersed Nuclear Elements, NFκB1= Nuclear Factor kappa B1, PPARγ= peroxisome proliferator-activated receptor-γ, RAAS= Renin Angiotensin Aldosteron System, TLR4= Toll Like Receptor-4, TNFα= tumor necrosis factor -α)*

distributed in vascular endothelial cells. ECE-1 is responsible for the production of endothelin-1, a peptide as a vasoconstriction function that helps regulate blood pressure. In Caucasian populations, promoter haplotype of the ECE-1b 839G/-338A gene is associated with high blood pressures (59).

Adducins as a cytoskeletal proteins encoded by alpha, beta, and gamma heterodimer is encoded by ADD1 gene, is one of the angiotensin RAAS sub- components. ADD1 is a candidate gene causes of high blood pressure. The effect of this protein other than increased renal sodium and water reabsorption also participates in the pathophysiology of hypertension. Research on a Chinese population found a correlation between rs4963 of the ADD1 gene and the risk of hypertension (59).

DNA METHYLATION AND LIPID PROFILE (TRIACYLGLYCEROL, HDL-C, LDL-C, AND CHOLESTEROL)

Dyslipidemia is characterized by a decrease in HDL-C and increase in LDL-C and/or increased concentration of triacylglycerol or triglyceride (TAG) and total cholesterol, which are risk factors for cardiovascular disease. Dyslipidemia is caused by life style and diet factors, such as unhealthy diet with compact dense energy diet, sedentary life style, or excess weight or obesity (60).

Genetic factors strongly influence lipid profile and lipid metabolism. Some GWASs identified genetic variants that influence lipid plasma, reaching 12% between different individuals. Epigenetic influences also play a role because of concurrent environmental factors that affect the expression of genes, especially the presence of methylation that affects transcription factors. Several studies reported that methylation in DNA specific genes are related to blood lipid concentrations, including methylation in the ApoB (61), ApoE, ABCG1 (62), and LPL (63) genes. A positive correlation exists between blood TAG and methylation in NPC1 (64) and IGF2 (65), as well as between blood TAG and methylation in some areas of CpG FAIM. In addition, a positive correlation exists between DNA methylation in PLA2G7 and BCL11A in female subjects but not in males (66). Another study identified two DNA methylations (i.e., ABCG1 and PHGDH) (67) that are associated with triglyceride levels. Methylation in PHGDH (cg14476101) affects triglyceride levels (68). Some methylations of DNA correlated with lipid profile are depicted in Figure 4.

The relationship between DNA methylation and candidate genes in blood HDL-C concentrations was studied. Results showed low DNA methylation in ABCA1(69), NPC1(62), MTHFR (61), LEP, LEPR(22), FAIM and ADIPOQ and high levels of gene methylation in LPL and DPP4 peripheral blood associated with high HDL-C plasma. No correlation exists between

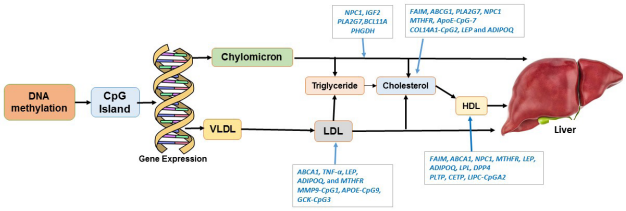

Figure 4: Methylation of DNA correlated with high levels of triglycerides, cholesterol, and LDL and low DNA level in the blood. (Abbreviation: *ABCA1= ATP binding Cassette sub family A1, ABCG1= ATP binding Cassette sub family G1, ADIPOQ= Adiponectin, ApoE= Apolipoprotein E, BCL11A= B-cell lymphoma 11 type A, CETP=cholesteryl ester transfer protein, COL14A1= Collagen Type XIV α1, DPP4 Dipeptidyl Peptidase4, FAIM = Fas apoptotic inhibitory molecule 2, GCK=Glucokinase , IGF2= Insulin-like growth factor-2, LEP= Leptin, LIPC=Lipase-C. LPL=Lipoprotein Lipase, MMP9=Matrix Metalloproteinase-9, MTHFR= methylene tetrahydrofolate reductase, NPC1= Niemann-Pick type C1, PHGDH= phosphoglycerate dehydrogenase, PLA2G7= Phopholipase-1 Group VII, PLTP= Phospholipid Transfer Protein, TNFα= Tumor necrosis factor α*)

HDL-C levels and DNA methylation in MCP-1, APOE, ABCG1, iNOS, TNF-α, TCF7L2, CD14, Et-1, HERV-W, IGF2, GALNT2, or HMGCR. Other studies have found different in gender influence between level of HDL-C and methylation of DNA in CETP, LIPC-CpGA2 and PLTP, showing a significant correlation in males but not in females (66).

Other studies on methylation in candidate genes correlated with total cholesterol showed that methylation of DNA occurs in blood and adipose tissue. Results showed that high methylation in MTFHR, FAIM, ABCG1 PLA2G7, and NPC1 and low methylation levels in DPP4 in peripheral blood result in increase of cholesterol in. In addition, high methylation levels in LEP, COL14A1-CpG2, ADIPOQ and ApoE-CpG-7 and low methylation levels of DNA in ApoE- CpG1, 2, 10, 12, 13, ABCG1-CpGC3, and TCF7L2-CpG27 are associated with high levels of Cholesterol in the blood. No correlation exists between total cholesterol and DNA methylation in ABCA1, BCL11A , GALNT2, IGF2,HMGCR, and M CP-1 (66).

Research on methylation of DNA in candidate genes found that methylation of DNA is correlated with level of LDL-C in visceral and placental adipose tissues. Results showed that high methylation levels DNA in ABCA1, ADIPOQ, MTHFR, LEP, LepR and TNF-α and in some areas of CpG in FAIM and low methylation levels in ADRB3 and NPC1 are associated with high LDL-C concentrations. LDL-C concentrations are also positively correlated with methylation in APOE-CpG9, GCK-CpG3 and MMP9-CpG1, and negatively correlated with methylation in MMP9-CpG4 and TCF7L2- CpG27. No association was found between LDL-C concentrations with methylation in ABCG1, CD14, Et-1, GALNT2, HMGCR, DPP4, HERV-W, IGF2, iNOS, IGF2, or MCP-1 (66,71).

Other studies in the CpG area in ABCG1, LINC00263

and SRBF1 found that methylation of DNA is positively correlated with lipoprotein ApoB concentrations, total serum triglycerides, and mono-unsaturated fatty acid (MUFA). Other groups in the CpG area in CPT1A and TXNIP are negatively correlated with lipoprotein ApoB, HDL-C, total serum triacylglycerol and MUFA levels (72).

EXERCISE AND DIET INFLUENCE DNA METHYLATION

Exercise and physical activity is a treatment strategy to increase lipid metabolism and improve lipid profile. In adipose tissue, healthy adult males with 6 months of controlled exercise show increased DNA methylation. Research on DNA methylation and mRNA expression in genes including histone deacetylase 4 (HDAC4) and nuclear receptor co-repressor 2 (NCOR2) demonstrated that silencing these genes in adiposity promotes lipogenesis. PGAC1a is a key regulator during physical exercise. Hypomethylation of the PGC1a promoter area upregulates mRNA expression in skeletal muscles. In addition, low methylation levels occur in the CpG coagulation factor II receptor like- 3 (F2RL3) area of smoking subjects. Methylation in this gene is also associated with coronary heart disease (73).

In a study using adipose tissue, 21 gen show differential methylation in the CpG locus in response to exercise. This study suggests that physcial activity induces genome-wide changes in methylation of DNA in human adipose tissue, potentially affecting adipocyte metabolism and maintain body weight. Non-nutritional diets, such as isoflavone phytoestrogen genistein and polyphenols found in plant, such as fruits, vegetables, herbs, spices, tea, dark chocolate, and wine, can also modify epigenetic signs and induce persistent changes in gene expression. The expression of altered genes induced by diet has a very low intensity and is difficult to distinguish. Some nutrients serve as ligands and bind to certain receptors, thus directly regulating the expression of the target gene (74). Polyunsaturated fatty acids influence PPARG gene expression, thereby affecting fat anabolism and oxidation or metabolism (75). The vitamins and some minerals such as cadmium, and zinc are also involved in chromatin modification and gene silencing by causing the biotinylation of histone H4 which inhibit DNMT activity (76). Alcohol consumption affects DNMT expression, leading to altered methylation patterns (77).

In general, a limitation of DNA methylation studies is their case–control design. The occurrence of diseases is specific to a certain period, and the mechanism by which DNA methylation affects the pathogenesis of the disease remains unclear.

CONCLUSION

Changes in the expression or supression of genes that alter metabolism, has a role as pathogenesis of metabolic syndrome. Exercise and nutrient factors influence the expression or suppression of genes through epigenetic mechanism, especially by methylation and demethylation in DNA promoter. The onset of metabolic syndrome can be inhibited by making lifestyle changes, such as regular exercise, lower stress and consumption of food that inhibits and prevents DNA methylation cause diseases.

REFERENCES

1. Carson C, Lawson HA. Epigenetics of metabolic syndrome. Physiol Genomics. 2018;50(11):947–55.
2. Panchal SK, Brown L. DNA Methylation in adipose tissue and metabolic syndrome. J Clin Med. 2020;9(9):2699.
3. Jaenisch R, Bird A. Epigenetic regulation of gene expression: How the genome integrates intrinsic and environmental signals. Nat Genet. 2003;33(3S):245–54.
4. Lopomo A, Burgio E, Migliore L. Epigenetics of obesity. Prog Mol Biol Transl Sci. 2016;140:151–84.
5. Hyun K, Jeon J, Park K, Kim J. Writing, erasing and reading histone lysine methylations. Exp Mol Med. 2017;49(4). e324
6. Vaiserman A, Lushchak O. Developmental origins of type 2 diabetes: Focus on epigenetics. Ageing Res Rev [Internet]. 2019;55(August):100957. doi:10.1016/j.arr.2019.100957
7. Samblas M, Milagro FI, Martнnez A. DNA methylation markers in obesity, metabolic syndrome, and weight loss. Epigenetics [Internet]. 2019;14(5):421–44. doi:10.1080/15592294.2019.1595297
8. Chaudhary N, Nakka KK, Maulik N, Chattopadhyay S. Epigenetic manifestation of metabolic syndrome and dietary management. Antioxidants Redox Signal. 2012;17(2):254–81.
9. Wang DD, Hu FB. Dietary fat and risk of cardiovascular disease: Recent controversies and advances. Annu Rev Nutr. 2017;37(June 2017):423–46.
10. Nitert MD, Dayeh T, Volkov P, Elgzyri T, Hall E, Nilsson E, et al. Impact of an exercise intervention on DNA methylation in skeletal muscle from first-degree relatives of patients with type 2 diabetes. Diabetes. 2012;61(12):3322–32.
11. Wahl S, Drong A, Lehne B, Loh M, Scott WR, Kunze S, et al. Epigenome-wide association study of body mass index, and the adverse outcomes of adiposity. Nature. 2017;541(7635):81–6.
12. Castellano-Castillo D, Moreno-Indias I, Fernandez-Garcia JC, Alcaide-Torres J, MorenoSantos I, Ocana L, et al. Adipose tissue LPL methylation is associated with triglyceride concentrations in the metabolic syndrome. Clin Chem. 2018;64(1):210–

8.
13. Van Dijk SJ, Peters TJ, Buckley M, Zhou J, Jones PA, Gibson RA, et al. DNA methylation in blood from neonatal screening cards and the association with BMI and insulin sensitivity in early childhood. Int J Obes [Internet]. 2018;42(1):28–35. doi:10.1038/ijo.2017.228
14. Dayeh T, Tuomi T, Almgren P, Perfilyev A, Jansson PA, de Mello VD, et al. DNA methylation of loci within ABCG1 and PHOSPHO1 in blood DNA is associated with future type 2 diabetes risk. Epigenetics. 2016 Jul 2;11(7):482–8.
15. Mamtani M, Kulkarni H, Dyer TD, Guring HHH, Neary JL, Cole SA, et al. Genome- and epigenome-wide association study of hypertriglyceridemic waist in Mexican American families. Clin Epigenetics [Internet]. 2016;8(1):1–14. doi:10.1186/s13148-016-0173-x
16. World Health Organization. Adolescent obesity and related behaviours: trends and inequalities in the WHO region 2002-2014. World Heal Organ Reg Off Eur. 2017;87.
17. Afshin A, Forouzanfar M. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med. 2017;377(1):13–27.
18. Crujeiras AB, Diaz-Lagares A. DNA Methylation in Obesity and Associated Diseases [Internet]. Epigenetic Biomarkers and Diagnostics. Elsevier Inc.; 2016. 313–329 p. doi:10.1016/B978-0-12-801899-6.00016-4
19. Yara S, Lavoie JC, Levy E. Oxidative stress and DNA methylation regulation in the metabolic syndrome. Epigenomics. 2015;7(2):283–300.
20. Candlera T, Kьhnenb P, Prenticea AM, Silvera M, Epigenetic regulation of POMC; implications for nutritional programming, obesity and metabolic disease, Frontier in Neorol, 2019, 54: 10073
21. Crujeiras AB, Campion J, Dнaz-Lagares A, Milagro FI, Goyenechea E,Abete I et al., Association of weight regain with specific methylation levels in the NPY and POMC promoters in leukocytes of obese men: A translational study, Regulatory Peptides, 2013,186: 1-6
22. Wryblewski A. Szemraj J, Świderska E, Drewniak K, Drzewoski J., Szemraj J, et al., Molecular Insight into the Interaction between Epigenetics and Leptin in Metabolic Disorders, Nutrients 2019, 11(8):1872
23. Main AM , Gillberg L, Jacobsen AL, Nilsson E, Gjesing AP, Hansen T, Pedersen O, RibelMadsen R and Vaag A, DNA methylation and gene expression of HIF3A: cross-tissue validation and associations with BMI and insulin resistance, Clin Epigen,2016, 8:89
24. Dick KJ, Nelson CP, Tsaprouni L, Sandling JK, Aпssi D, Wahl S, et al. DNA methylation and body-mass index: A genome-wide analysis. Lancet. 2014;383(9933):1990–8.
25. Cordero P, Campion J, Milagro FI, Goyenechea E, Steemburgo T, Javierre BM, et al. Leptin and TNF-alpha promoter methylation levels measured by MSP could predict the response to a low-calorie diet. J Physiol Biochem. 2011;67(3):463–70.
26. Milagro FI, Gymez-Abellбn P, Campiyn J, Martнnez JA, Ordovбs JM, Garaulet M. CLOCK, PER2 and BMAL1 DNA methylation: Association with obesity and metabolic syndrome characteristics and monounsaturated fat intake. Chronobiol Int. 2012;29(9):1180–94.
27. Choi JH, Jung Park M, Kook WK, Yoon HC, Sun HP, Won GA, et al. Molecular mechanism of hypoxia-mediated hepatic gluconeogenesis by transcriptional regulation. FEBS Lett. 2005;579(13):2795–801.
28. Koh IU, Choi NH, Lee K, Yu HY, Yun JH, Kong JH, et al. Obesity susceptible novel DNA methylation marker on regulatory region of inflammation gene: Results from the Korea Epigenome Study (KES). BMJ Open Diabetes Res Care. 2020;8(1):1–10.
29. Wahl S, Drong A, Lehne B, Loh M, Scott WR, Kunze S, et al. Epigenome-wide association study of body mass index, and the adverse outcomes of adiposity. Nature. 2017;541(7635):81–6.
30. Krause C, Sievert H, Geißler G, Grohs M, El Gammal AT, Wolter S, et al., Critical evaluation of the DNA-methylation markers ABCG1 and SREBF1 for Type 2 diabetes stratification, Epigenomics, 2019, 11(8): 885-897. doi: 10.2217/epi-2018-0159
31. Mendelson MM, Marioni RE, Joehanes R, Liu C, Hedman EK, Aslibekyan S, et al. Association of body mass index with DNA methylation and gene expression in blood cells and relations to cardiometabolic disease:A mendelian randomization approach. PLoS Med. 2017;14(1):1–30.
32. Dhana K, Braun KVE, Nano J, Voortman T, Demerath EW, Guan W, et al. An epigenome-wide association study of obesity-related traits. Am J Epidemiol. 2018;187(8):1662–9.
33. Pedroso JAB, Ramos-Lobo A, Donato J. SOCS3 as a future target to treat metabolic disorders. Hormones. 2019; Jun;18(2):127-136. doi: 10.1007/s42000-018-0078-5.
34. Xu K, Zhang X, Wang Z, Hu Y, Sinha R. Epigenome-wide association analysis revealed that SOCS3 methylation influences the effect of cumulative stress on obesity. Biol Psychol. 2018;131:63–71.
35. Ling C, Rцnn T. Epigenetics in human obesity and type 2 diabetes. Cell Metab. 2019;29(5):1028–44.
36. Davegerdh C, Broholm C, Perfilyev A, Henriksen T, Garcна-calzyn S, Peijs L, et al. Abnormal epigenetic changes during differentiation of human skeletal muscle stem cells from obese subjects. BMC Med. 2017;15(39):1–27.
37. Lother A, Bondareva O, Saadatmand AR, Pollmeier L, Hдrdtner C, Hilgendorf I, et al. Diabetes changes gene expression but not DNA methylation in

cardiac cells. J Mol Cell Cardiol. 2021;151(October 2020):74–87.
38 Hafez SM, Abou-youssef HES, Awad MAK, Kamel SA, Youssef RN, Elshiekh SM, et al. Insulin-like growth factor binding protein 1 DNA methylation in type 2 diabetes. Egypt J Med Hum Genet. 2021;22:29.
39. Willmer T, Johnson R, Louw J, Pheiffer C. Blood-Based DNA Methylation biomarkers for type 2 diabetes: potential for clinical applications. Front Endocrinol (Lausanne). 2018;9(December):1–16.
40. Kuroda A, Rauch TA, Todorov I, Ku HT, Al-Abdullah IH, Kandeel F, et al. Insulin gene expression is regulated by DNA methylation. PLoS One. 2009;4(9):e6953. doi: 10.1371/journal.pone.0006953.
41. Giacchetti G, Faloia E, Taccaliti A, Morosini PP, Arnaldi G, Soletti F, et al. Decreased expression of insulin-sensitive glucose transporter mRNA (GLUT-4) in adipose tissue of non-insulin-dependent diabetic and obese patients: Evaluation by a simplified quantita PCR assay. J Endocrinol Invest. 1994;17(9):709–15.
42. Ozcan U, Cao Q, Yilmaz E, Lee A-H, Iwakoshi NN, Ozdelen E, et al. endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. Science (80-). 2004;306(October):457–61.
43. Schmidt MV, Brüne B, Von Knethen A. The nuclear hormone receptor PPARγ as a therapeutic target in major diseases. Sci World J. 2010;10:2181–97.
44. Yang BT, Dayeh TA, Kirkpatrick CL, Taneera J, Kumar R, Groop L, et al., Insulin promoter DNA methylation correlates negatively with insulin gene expression and positively with HbA1c levels in human pancreatic islets, Diabetologia. 2011; 54(2): 360–367.
45. Małodobra-Mazur M, Cierzniak A, Kaliszewski K, Dobosz T., PPARG Hypermethylation as the First Epigenetic Modification in Newly Onset Insulin Resistance in Human Adipocytes, Genes (Basel). 2021 Jun; 12(6): 889.
46. Hall E., Dayeh T, Kirkpatrick CL, Wollheim CB, Nitert MD, Ling C, DNA methylation of the glucagon-like peptide 1 receptor (GLP1R) in human pancreatic islets, BMC Med Genet. 2013; 14: 76.
47. Hall E, Dekker Nitert M, Volkov P, Malmgren S, Mulder H, Bacos K, et al. The effects of high glucose exposure on global gene expression and DNA methylation in human pancreatic islets. Mol Cell Endocrinol [Internet]. 2018;472:57–67. doi:10.1016/j.mce.2017.11.019
48. Elliott HR, Walia GK, Duggirala A, Groom A, Reddy SU, 3 Chandak GR et al., Migration and DNA methylation: a comparison of methylation patterns in type 2 diabetes susceptibility genes between indians and europeans, J Diabetes Res Clin Metab. 2013; 2: 6.
49. Abderrahmani A, Yengo L, Caiazzo R, Canouil M, Cauchi S, Raverdy V, et al. Increased hepatic PDGF-AA signaling mediates liver insulin resistance in obesity-associated type 2 diabetes. Diabetes. 2018;67(7):1310–21.
50. Volkov P, Bacos K, Ofori JK, Esguerra JLS, Eliasson L, Runn T, et al. Whole-Genome bisulfite sequencing of human pancreatic islets reveals novel differentially methylated regions in type 2 diabetes pathogenesis. Diabetes. 2017 Apr 1;66(4):1074–85.
51. Nakatochi M, Ichihara S, Yamamoto K, Naruse K, Yokota S, Asano H, et al. Epigenomewide association of myocardial infarction with DNA methylation sites at loci related to cardiovascular disease. Clin Epigenetics. 2017;9(1):1–9.
52. Zhuo C, Feng M, Andrew DP, John ML, Lingxiao Z, Dustin ES, et al. Epigenomic profiling reveals an association between persistence of DNA methylation and metabolic memory in the DCCT/EDIC type 1 diabetes cohort. Proc Natl Acad Sci U S A. 2016;113(21):E3002–11.
53. Amenyah SD, Ward M, McMahon A, Deane J, McNulty H, Hughes C, et al. DNA methylation of hypertension-related genes and effect of riboflavin supplementation in adults stratified by genotype for the MTHFR C677T polymorphism. Int J Cardiol [Internet]. 2021;322(xxxx):233–9. doi:10.1016/j.ijcard.2020.09.011
54. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. 2017ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults a report of the American College of Cardiology/American Heart Association Task Force on Clinical pr. Vol. 71, Hypertension. 2018. 13–115 p.
55. Stoll S, Wang C, Qiu H. DNA methylation and histone modification in hypertension. Int J Mol Sci. 2018;19(4):1–17.
56. Gonzalez-Jaramillo V, Portilla-Fernandez E, Glisic M, Voortman T, Bramer W, Chowdhury R, et al. The role of DNA methylation and histone modifications in blood pressure: a systematic review. J Hum Hypertens [Internet]. 2019;33(10):703–15. doi:10.1038/s41371-019-0218-7
57. Wise IA, Charchar FJ. Epigenetic modifications in essential hypertension. Int J Mol Sci. 2016;17:451.
58. Mashasi D, Kiyofumi S. The role of DNA methylation in Hypertension. Adv Exp Med Biol. 2016;491–511.
59. Han L, Liu Y, Duan S, Perry B, Li W, He Y. DNA methylation and hypertension: Emerging evidence and challenges. Brief Funct Genomics. 2016;15(6):460–9.
60. Mittelstraß K, Waldenberger M. DNA methylation in human lipid metabolism and related diseases. Curr Opin Lipidol. 2018;29(2):116–24.
61. Chena HC, Chena YZ, Wangb CH, Lina FJ,The

nonalcoholic fatty liver disease-like phenotype and lowered serum VLDL areassociated with decreased expression and DNA hypermethylation of hepatic ApoB in male offspring of ApoE deficient mothers fed a with Western diet, J Nutr Biochem, 2020, 77: 108319
62. Qin X, Li J, Wu T, Wu Y, Tang X, Gao P, et al., Overall and sex-specific associations between methylation of the ABCG1 and APOE genes and ischemic stroke or other atherosclerosis-related traits in a sibling study of Chinese population, Clin Epigenet , 2019, 11:189
63. Castellano-Castillo D, Moreno-Indias I, Fernández-García IC, Alcaide-Torres J, MorenoSantos I, Ocaca L et al. , Adipose Tissue LPL Methylation is Associated with Triglyceride Concentrations in the Metabolic Syndrome , Clin Chem, 2018, 64 (1): 210–218,
64. Afzali M, Nakhaee A, Tabatabaei SP, Tirgar-Fakheri K, Hashemi M, Aberrant Promoter Methylation Profile of Niemann-Pick Type C1 Gene in Cardiovascular Disease, Iran Biomed J. 2013 Apr; 17(2): 77–83
65. Deodati A. Inzaghi E. Liguori A. Puglianiello A. Germani D. Brufani C. et al., IGF2 Methylation Is Associated with Lipid Profile in Obese Children, Horm Res Paediatr 2013;79:361-367
66. Braun KVE, Voortman T, Dhana K, Troup J, Bramer WM, Troup J, et al. The role of DNA methylation in dyslipidaemia: A systematic review. Prog Lipid Res [Internet]. 2016;64:178–91. doi:10.1016/j.plipres.2016.10.002
67. Truong V, Huang S, Dennis J, Lemire M, Zwingerman N, Aɲssi D4, Kassam I., et al., Blood triglyceride levels are associated with DNA methylation at the serine metabolism gene PHGDH, Scientific Reports , 2017, 7: 11207
68. Truong V, Huang S, Dennis J, Lemire M, Zwingerman N, Aɲssi D, et al. Blood triglyceride levels are associated with DNA methylation at the serine metabolism gene PHGDH. Sci Rep. 2017;7(1):1–13.
69. Miroshnikova VV, Panteleeva AA, Pobozheva IA, Razgildina ND, Polyakova EA, Markov AV et al., ABCA1 and ABCG1 DNA methylation in epicardial adipose tissue of patients with coronary artery disease, BMC Cardiovasc Dis, 2021; 21: 566
70. Bezerra HS, de Assis CS, dos Santos Nunes MK, Evangelista IWQ, Filho JM, Gomes CNAP et al., The MTHFR promoter hypermethylation pattern associated with the A1298C polymorphism influences lipid parameters and glycemic control in diabetic patients, Diabetol Metab Syndr. 2019; 11: 4.
71. Lima RPA, Ribeiro MR, de Farias Lima KQ, Sena EA de, de Oliveira Costa D, Luna RCP, et al. Methylation profile of the ADRB3 gene and its association with lipid profile and nutritional status in adults. Biol Res [Internet]. 2019;52(1):21. doi:10.1186/s40659-019-0226-7
72. Gomez-Alonso M del C, Kretschmer A, Wilson R, Pfeiffer L, Karhunen V, Seppälä I, et al. DNA methylation and lipid metabolism: An EWAS of 226 metabolic measures. Clin Epigenetics. 2021;13(1):1–19.
73. He Z, Zhang R, Jiang F, Hou W, Hu C. Role of genetic and environmental factors in DNA methylation of lipid metabolism. Genes Dis [Internet]. 2018;5(1):9–15. doi:10.1016/j.gendis.2017.11.005
74. Mariman ECM. Nutrigenomics in perspective. Pharmacogenomics. 2007;8(5):421–4.
75. Baharanchi EM, Sarabi MM, and Naghibalhossaini F, Effects of Dietary Polyunsaturated Fatty Acids on DNA Methylation and the Expression of DNMT3b and PPAR α Genes in Rats, Avicenna J Med Biotechnol. 2018 Oct-Dec; 10(4): 214–219.
76. Vidal AC, Semenova V, Darrah T, Vengosh A, Huang Z, King K, et al., Maternal cadmium, iron and zinc levels, DNA methylation and birth weight, BMC Pharmacology and Toxicology (2015) 16:20
77. Miozzo F, Arnould H, de Thonel A, Schang A, Sabéran-Djoneidi D, Baudry A, et al., Alcohol exposure promotes DNA methyltransferase DNMT3A upregulation through reactive oxygen species-dependent mechanisms, Cell Stress Chaperones. 2018 Jan; 23(1): 115–126.