Review

The effects of vitamins and dietary pattern on epigenetic modification of non-communicable diseases

A review

Editor's Choice

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Abstract: *Background:* Non-communicable diseases (NCDs) have received more attention because of high prevalence and mortality rate. Besides genetic and environmental factors, the epigenetic abnormality is also involved in the pathogenesis of NCDs. Methylation of DNA, chromatin remodeling, modification of histone, and long non-coding RNAs are the main components of epigenetic phenomena. *Methodology:* In this review paper, the mechanistic role of vitamins and dietary patterns on epigenetic modification was discussed. All papers indexed in scientific databases, including PubMed, Scopus, Embase, Google Scholar, and Elsevier were searched during 2000 - 2021 using, vitamins, diet, epigenetic repression, histones, methylation, acetylation, and NCDs as keywords. *Results:* The components of healthy dietary patterns like Mediterranean and dietary approaches to stop hypertension diets have a beneficial effect on epigenetic hemostasis. Both quality and quantity of dietary components influence epigenetic phenomena. A diet with calorie deficiency in protein content and methyl-donor agents in a long time, with a high level of fat, disrupts epigenetic hemostasis and finally, causes genome instability. Also, soluble and insoluble vitamins have an obvious role in epigenetic modifications. Most vitamins interact directly with methylation, acetylation, and phosphorylation pathways of histone and DNA. However, numerous indirect functions related to the cell cycle stability and genome integrity have been recognized. *Conclusion:* Considering the crucial role of a healthy diet in epigenetic homeostasis, adherence to a healthy dietary pattern containing enough levels of vitamin and avoiding the western diet seems to be necessary. Having a healthy diet and consuming the recommended dietary level of vitamins can also contribute to epigenetic stability.

Keywords: Acetylation, diet, epigenetic repression, histones, Methyl-CpG-binding protein, methylation, NCDs, vitamins

Abbreviations

ARE	Antioxidant-responsive element
ARTs	ADP-ribosyltransferases
BHMT	Betaine-homocysteine methyltransferases
CBS	Cystathionine-synthase
CREB proteins	cAMP-response element binding proteins
CYP2R1	Cytochrome P450 family 2 subfamily R member 1
CYP27B1	Cytochrome P450 family 27 subfamily B member 1
DNAm	DNA methylation
DNMTs	DNA methyltransferases
DNMT1	DNA methyltransferase 1
FAD	Flavin adenine dinucleotide
FAS	Fatty acid synthase
Fgf-23	Fibroblast growth factor 23
FMN	Flavin mononucleotide
FOXO proteins	Forkhead box O proteins
Gas6	Growth arrest-specific
GATA-4	GATA-binding protein 4
GRIA1	Glutamate inotropic receptor AMPA-type subunit 1
HATs	Histone acetyltransferases
HDACs	Histone deacetyltransferase
HIF1a	Hypoxia-inducible factor 1a
HKMTs	Histone lysine methyltransferases
iNKT	Invariant natural killer T
IGF1R	Insulin-like growth factor 1 receptor
LSD1	Lysine-specific demethylase 1
LDLR	Low-density lipoprotein receptor
LMX1A	LIM Homeobox transcription factor 1 alpha
MLH1	MutL homolog 1

MS	Methionine synthase
MSR	Methionine synthase reductase
NA	Nicotinic acid
NAM	Nicotinamide
NCDs	Non-communicable diseases
NF-kB	Nuclear factor-kB
Ngn2	Neurogenin 2
Nrf1	Nuclear factor-E2-related factor-1
Nurr1	Nuclear receptor related 1
Osx	Osteoblast differentiation regulator osterix
PARP1	Poly ADP-ribose polymerase 1
PITX3	Paired like homeodomain 3
PGC1-α	Peroxisome proliferator gamma coactivator 1-α
PHD2	Domain-containing protein 2
PARPs	Poly (ADP-ribose) polymerase
PITX3	Paired Like Homeodomain 3
PPARγ	Peroxisome proliferator-activated receptor γ
PRMTs	Protein arginine methyltransferases
ProS	Protein S
RXR	Retinoid X receptor
SAM	S-adenosyl-methionine
SHMT	Serin-hydroxymethyltransferase
SIRTs	Sirtuins
SIRT1	Sirtuin 1
SREBF1	Sterol regulatory element-binding transcription factor 1
STAT3	Signal transducer and activator of transcription 3
TAM	Tyro3, Axl, MerTK
mTHF	Methylenetetrahydrofolate
TET1-3	Ten-eleven-translocation 3
VDR	Vitamin D receptor
WHO	World Health Organization

Introduction

Nowadays, non-communicable diseases (NCDs), including diabetes, cardiovascular diseases, cancer, stroke, chronic obstructive pulmonary diseases, dementia, cognitive decline, and obesity account for a crucial public health problem worldwide [1, 2, 3]. Annually, NCDs have imposed a considerable burden on health care systems and their control seems to be a priority [4]. Besides genetic determinants, environmental factors, such as lifestyle changes, including unhealthy diet and physical inactivity, and air pollution, stressor factors, smoking, exposure to carcinogenic components, and epigenetic disturbance are categorized as the main causes of NCDs [5, 6]. Changes in the dietary pattern characterized by shifting from consumption of a diet rich in whole grains, raw and fresh fruits, and vegetables to the western diet with high content of caloric foods, sugar, salt, and fat are considered as the main risk factors of NCDs [7]. Adherence to the western diet over time can result in deficiencies in vitamins and minerals and potentially worsens the status of patients with NCDs [8, 9]. There is enough evidence showing that patients with NCDs are at risk of certain types of vitamin deficiencies [10]. Deficiencies of vitamin D in patients with CVD, vitamins B9, B12, A, C, and E in patients with type 2 diabetes, vitamins D and E in patients with acute respiratory distress syndrome (ARDS), vitamins B12 and D in cancer patients, and also vitamins D and A in patients with renal diseases have been also reported [11, 12, 13, 14, 15, 16, 17, 18].

One of the potential mechanisms related to the role of micronutrients deficiency in the pathogenesis of NCDs is attributed to the role of micronutrients in various aspects of epigenetic pathways [19, 20, 21]. Vitamins and trace elements are defined as epigenetic modifiers [22]. High mortality and morbidity rates among patients with NCDs in the world have been attributed to disorders in the immune system and malnutrition [10, 23, 24, 25]. Therapy with micronutrients in patients with NCDs is used to improve nutritional status, strengthen immune system, and decrease circulatory inflammatory cytokines via epigenetic modification [26, 27, 28, 29, 30]. Given the high prevalence of NCDs and the evidence about the role of macronutrients and micronutrients on the epigenetic pathway, on the other hand, due to lack of study about the role of vitamins and dietary patterns in epigenetic modification, this review paper was done to present a comprehensive mechanistic role of vitamins and dietary patterns in modulation of epigenetic pathways in detail.

Materials and methods

In this review paper, the papers published in scientific databases, including PubMed, Scopus, Embase, Google Scholar, and Elsevier were searched using medical subject headings (MeSH) keywords, such as vitamins, diet, epigenetic repression, histones, methylation, acetylation, and NCDs, and the obtained results were discussed. The search was limited to the published studies in English conducted during 2000–2021.

Results and discussion

Epigenetic phenomena

Epigenetic changes potentially refer to any modification in gene expression caused by various factors, including

environmental factors with no changes in DNA sequencing and genetic information [31, 32]. In other words, any inherited or acquired but reversible changes in gene expression are referred to as the epigenetic concept [33]. Modification of histone, DNA methylation (DNAm) in gene promoter sequences, chromatin remodeling, and long non-coding RNAs are the main recognized epigenetic modification processes [34, 35, 36, 37, 38]. Overall, these reactions influence all stages of the cell cycle, including replication, transcription, translation, and also DNA and RNA repair process [39].

Histones have been defined as protein components of nucleosomes interacting with DNA base pairs [40]. Methylation, acetylation, and phosphorylation of amino acid tails of histones are among post-translational changes in the expressed genes that are considered epigenetic modifications [41, 42]. Ubiquitination and biotinylation of N-terminal histone tails and ADP-ribosylation are other modifications in chromatin structure [43]. In ubiquitination of histone, ubiquitin molecules are transported to histone core proteins, such as H2A and H2B, and are involved in activation or suppression of gene expression [43, 44]. Besides histones, methylation of DNA is dependent on methyl donor molecules [45]. DNAm modifies gene expression, plasticity of DNA, and chromosome integrity in the cell cycle via providing methyl groups to cytosine sites [46]. In various cells or tissues, DNA methyltransferase (DNMTs) enzymes methylate carbon 5 of cytosine in CpG dinucleotide in the promoter region of genes [47]. Among different types of DNMTs, including DNMT1, DNMT2, DNMT3a, 3b, and 3L, some of them have catalytic activity. Any alternation in normal DNAm patterns (both global and gene-specific) leads to cancer development, tumorigenesis, and mortality [48].

NCDs and epigenetic disturbance

According to the report published by the world health organization (WHO), 60% of the mortality rate in the world is attributed to NCDs and as estimated, this rate will be increased by 2025 [49]. Thus, discovering an effective approach to control and manage NCDs should be a priority [50]. In spite of the high prevalence of NCDs worldwide, especially in low- and middle-income countries, its mechanistic etiology has not been understood completely. Various potential factors, such as obesity, inflammation, and disruption of endocrine and immune systems, and epigenetic hemostasis have been recognized in this regard. Recently, epigenetic modification has received more attention as one of the crucial etiological factors in development of NCDs [6, 51]. A close relationship has been reported between dysregulation of epigenetic processes and NCDs. Surprisingly, not only epigenetic but also environmental factors aggregate the status of patients with NCDs. In other words, for example, exposure of cancer patients to environmental stressors during life-span has resulted in an alternation in epigenetic patterns [52]. Epigenetic changes result in the incidence of chronic diseases (e.g., diabetes, obesity, and cancer) by different mechanisms [53, 54, 55, 56].

Dietary patterns and epigenetic modifications

A healthy dietary pattern is defined as the diet with high contents of vegetables, fruits, whole grains, low- or non-fat dairy, seafood, legumes, and nuts; moderate in alcohol; low in red and processed meat, and sugar-sweetened foods, drinks, and refined grains [57, 58]. It has been shown that dietary factors are involved in all relevant pathways of genome integrity and DNA stability, including DNA synthesis/repair, apoptosis, and detoxification of carcinogenesis [59]. Adherence to an unhealthy diet alters epigenetic patterns via disruption of epigenetic components, such as methylation and acetylation of DNA and histones, etc., which finally contributes to the incidence of NCDs [60]. According to the evidence-based medicine databases, a calorie-dense diet disrupts epigenetic pathways via decreasing DNAm by about 50% in the Zfp423 promoter region due to being rich in CpG sites [61, 62]. In contrast, calorie restriction while maintaining optimal nutrition intake during weight loss programs results in a decrease in the incidence of chronic diseases and aging by modifying the function of proteins involved in modification pathways of histone, such as CREB-binding protein and sirtuins that induce epigenetic phenomena and modify methylation of various genes in adipose tissue [63, 64].

Not only calorie intake but also a component of macronutrients influences epigenetic regulation. Any change in the content of the recommended macronutrients alters DNAm and other epigenetic-related pathways [65, 66, 67]. A low-protein diet that contains a little amount of especially histidine, methionine, serine, and glycine disrupts protein metabolism and results in various chronic diseases by downregulation of DNAm, acetylation and methylation of histone, and chromatin remodeling [50, 51, 52, 68, 69, 70]. Also, protein deficiency in the diet decreases specific cytosine's methylation in the promoter region of hepatic peroxisome proliferator-activated receptor alpha (PPAR-α), insulin-like growth factor 2(IGF2), and H19 genes expression and alters acetylation and methylation pathways of histone regulating the metabolism of amino acids in the liver [67, 71, 72].

Another dietary factor studied is a diet deficient in methyl-donor agents. Due to the role of methyl agents as substrate, cofactor, or activator of enzymes in epigenetic pathways of gene expression, deficiency of methyl-donors influences various cellular pathways [26]. According to the studies, lack of methyl donors contributes to the incidence of several abnormalities, such as steatosis (influencing methylation of fatty acid synthase) [73, 74, 75], abnormality of growth and brain functions (downregulation of the signal transducer and activator of transcription 3 (STAT3) through influencing miR-124) [76], heart diseases (disturbance in methylation or acetylation of peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α) [77]), and difficulty in learning and memorization (hypermethylation and decreasing expression of glutamate ionotropic receptor AMPA type subunit 1(GRIA1) gene) [78].

Another dietary factor disturbing epigenetic signature is a diet high in fat content. According to the studies, a high-fat diet besides inducing overexpression of genes involved in obesity and enhancing appetite [79, 80] can modify the epigenetic pattern, such as dysregulation of acetylation and deacetyltransferase activities of histones [81].

Besides, quality and quantity of diet, and also abundance of dietary components influence epigenetic phenomena [82]. It has been demonstrated that infants who were born in rainy seasons where rich foods were plentiful compared to those who were born in dry seasons, had a higher level of methylation in DNA and histones. Despite this, in children who had been grown up in famine; the trend of their growth slowed down due to the low level of DNAm of genes involved in growth and development, and growth was declined [83]. Based on explanations, having enough, balanced, and varied diets meeting both quantitative and qualitative needs of people is suggested. Figure 1 shows the interaction of dietary patterns with epigenetic modifications.

The role of vitamins in epigenetic signatures

Table 1 shows the main functions of vitamins in the body. It has been indicated that due to the gene-nutrient interaction of vitamins, marginal deficiency of vitamins acts as a risk factor for the incidence of chronic diseases [84]. Micronutrients especially are required for DNA stability and insufficient dietary intake of micronutrients leads to DNA breakage and genomic damage [33, 85]. Considering enough evidence about the crucial role of vitamins in epigenetic regulation, the role of insoluble and soluble vitamins will be discussed in detail in the following.

Vitamin A

Vitamin A regulates the expression of various genes by interacting with nucleus receptors [118]. The retinoic acid form of vitamin A regulates gene expression through two families of receptors, including retinoid acid receptor (RAR) and retinoid X receptor (RXR) [119]. These receptors are involved in DNAm and acetylation pathways of histone [120, 121]. In the nucleus, a specific sequence of target genes is induced via the interaction of the related ligands of transcription factors with the complex of RAR/RXR [119, 122]. One of the coactivators of RAR-α is histone lysine demethylase named PHF8. PHF8 is an iron-dependent enzyme and acts in monomethyl and dimethyl states on histones in response to stem cells to retinoic acid [123].

A diet deficient in vitamin A results in improper methylation of the GATA binding protein 4 (GATA-4) gene in the promoter region and is accompanied by various defects [124, 125]. Vitamin A deficiency also disrupts acetylation of histone via dysregulation of CREB-binding protein as one of the histone acetyltransferases induced by RAR-α [126]. Dietary intake of vitamin A from animal and plant foods in the recommended amount results in epigenetic integrity and genome stability.

Vitamin D

Vitamin D deficiency is important in the pathogenesis of various NCDs, such as diabetes, obesity, metabolic syndrome, coronary heart diseases, cancers, chronic lung disorders, inflammatory disorders like rheumatoid arthritis and systemic lupus erythematosus, Crohn's disease, and multiple sclerosis [127, 128] via various mechanisms, such as epigenetic disturbance [120]. Vitamin D receptors (VDRs) modify histone proteins and DNAm in the promoter region of the genome [129, 130].

VDR exists as heterodimers with RXR, and the complex of VDR/RXR binds to particular sequences of target genes on the promoter region of transcription pathways [91, 131]. VDRs are typically composed of heterodimers with RXRs in the nuclear form and bind to specific sites in genome sequencing to regulate gene expression [88, 132].

VDR/RXR dimer is involved in the regulation of epigenetic factors, such as histone acetyltransferases (HATs) during transcription [133]. Indeed, VDRs interact with receptors inducing HATs and histone deacetylases (HDACs) [41]. VDRs also interact with forkhead box (FOXO) proteins and their regulator sirtuin 1 and enhance their functions in the promoter region of VDRs target genes [134]. Due to scattering of VDRs in many tissues, such as the heart, pancreatic cells, immune cells, colon, breast, etc., they exert biological function by activation or

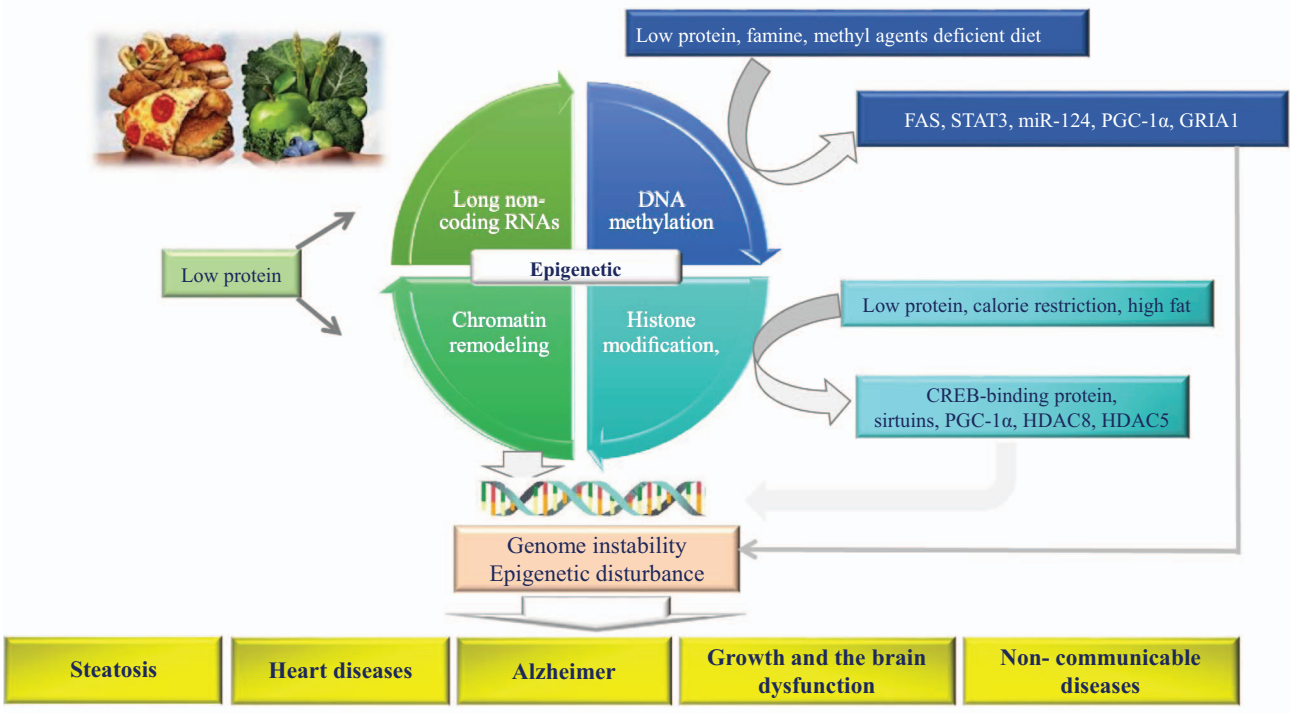

Figure 1. Effects of dietary components on epigenetic signature. FAS: Fatty acid synthase; STAT3: Signal transducer and activator of transcription 3; PGC1-α: Peroxisome proliferator gamma coactivator 1-α; GRIA1: Glutamate inotropic receptor AMPA-type subunit 1; HDAC8: Histone deacetylase 8; HDAC5: Histone deacetylase 8.

suppression of genes involved in the cell cycle [135, 136]. These functions include the regulation of elements involved in metastasis, tumor angiogenesis, DNA damage, growth factors, and apoptosis [137, 138].

1, 25 $(OH)_2$ vitamin D3 or analogs of vitamin D, such as CYP27B1 and CYP2R1 [139], act as ligands of VDR and exert their effects on gene expression by transportation from the cytosol to nucleus [140]. For example, dysfunction of CYP27B1 as a mutation leads to hereditary type 1 rickets [141].

Vitamin D improves inflammation by controlling the expression of nuclear factor kappa-B (NF-κB)-related cytokines [142]. VDR inhibits NF-κB function through SIRT1 and 1,25D signaling, confirming the role of 1,25D in deacetylation of NF-κB through interaction with SIRT1 [143]. Deficiency of vitamin D decreases mRNA levels of NF-kB, IGF1R, p53, and Fgf-23 that are involved in strengthening of immunity and prevention of aging [144].

Deficiency of vitamin D also leads to changes in DNAm of locus-specific sites and telomerase activity related to aging; however, it has been shown that supplementation of vitamin D reverses these dysfunctions [145, 146, 147]. VDR upregulates the p21 (waf1/cip1) gene, which in turn suppresses the cell cycle and C/EBP gene-regulating cellular senescence and differentiation [41, 131]. Another effect of vitamin D in epigenetic modification is related to induction of apoptosis by enhancing the number of invariant natural killer T (iNKT) cells [148].

Vitamin E

Vitamin E was recognized for the first time in 1922 [149]. One of the epigenetic functions of vitamin E is DNAm in the DNA repair pathway. Vitamin E at non-toxic concentration enhances expression of DNA repair genes of MutL homolog 1(MLH1) and DNMT1 and marker of overall methylation, long-interspersed element 1(LINE-1) [150]. MLH1 belongs to (mismatch repair) MMR proteins and is involved in the base excision repair system. In the damaged DNA, MLH1 induces apoptosis and cell death via influencing the NAD^+-dependent deacetylases of SIRT1 and PARP1 as components of DNMTs [151, 152]. A diet with a low level of vitamin E leads to an increase in the peroxidation of lipids in the cell membrane. Due to the limited placental transportation and low tissue concentrations of vitamin E, newborn infants are considered as the group at risk of vitamin E deficiency [153].

Table 1. The biological importance of vitamins in the body

Item	Fat/water soluble	RDA/DRI recommended doses	Biological forms	Sources	Role	Deficiency symptoms	Ref
Vitamin A	Fat-soluble	700–900 RAE/day	Retinol, Retinal, Retinoic acid	Animal foods: such as turkey, cod liver, butter. Plant foods: yellow-orange plants such as potato, squash, kale, carrot	Vision, cellular proliferation, differentiation, growth immunogenicity	Growth retardation, weakening of the immune system, visual impairment	[86, 87]
Vitamin D	Fat-soluble	15 μ/day	25-(OH)D, 1, 25 (OH)D	Dermal synthesis and foods such as fatty fish	Regulation of calcium homeostasis and bone metabolism, proliferation, differentiation, cell growth, apoptosis, mitochondrial respiration	Dysfunction of organs, inflammation, attenuating the immunity system	[88, 89, 90, 91]
Vitamin E	Fat-soluble	15 α-TE (mg)/day	Tocopherol, Tocotrienols	Plant oils such as olive oils, sunflower oil, and nuts	Anti-aging, anti-cancer, anti-diabetic, protection against cardiovascular and liver diseases	Inflammation	[92]
Vitamin K	Fat-soluble	90–120 μg/day	Phylloquinone, Menaquinone, Menadione	Dark green vegetables, plant chlorophylls, fermented products by bacteria	Coagulation, bone development, cardiovascular health	Bleeding, osteoporosis poor bone development, cardiovascular disease	[93, 94]
Vitamin B2	Water-soluble	0.3–1.6 mg/day	Flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN)	Green beans, banana, asparagus, milk and related products	Energy metabolism, activation of vitamin B6, normal growth, reproduction, good performance, antioxidant effect, cardioprotective properties, strengthen the immune system	Anemia, migraines, thyroid abnormality, cataract	[26, 95, 96]
Vitamin B3	Water-soluble	2–18 mg/day	Nicontinamide adenine nucleotide (NAD), nicotinamide (NAM), nicotinic acid (NA)	Dairy products, lean meat and poultry, fish, yeasts, grains, and peanuts	Energy metabolism, cellular regulatory pathways	Dermatitis, vomiting, diarrhea, headache, fatigue, memory loss	[97, 98]
Vitamin B6	Water-soluble	0.1–2.0 mg/day	Pyridoxine (PN), pyridoxal (PL), pyridoxamine (PM)	Animal foods such as meat and fish, nuts, seeds, and vegetables such as broccoli, spinach, green peas, asparagus and potatoes	Transamination, racemization, α-decarboxylation, β- and γ-eliminations, aldol cleavage reactions, synthesis of serotonin and dopamine. Activation of cystathionine – synthase (CBS)	Homocysteinemia homocystinuria	[99, 100, 101, 102]
Vitamin B9	Water-soluble	65–600 μg	Folic acid	Liver, dark green leafy vegetables, cereals, orange, milk, yeast, and mushroom	cellular pathways including DNA synthesis and stability and DNA and RNA methylation	Depression, cancers, heart diseases, birth defects	[39, 103, 104, 105]
Vitamin B12	Water-soluble	0.4–2.8 μg/day	Cyanocobalamin, Methylcobalamin	Milk, fish, egg, selfish, meat, enriched cereals, fermented beans, vegetables, tea	Coenzyme of methionine synthase, methylmanoyl-CoA mutase enzymes	Megaloblastic anemia and neurological disorders, vascular dementia, mood disturbances, homocysteinemia	[106, 107, 108, 109, 110, 111, 112, 113, 114]
Vitamin C	Water-soluble	15–120 mg/day	Ascorbate, dehydroascorbate	Fresh and raw fruits and green leaves vegetable	synthesis of catecholamine and carnitine, differentiation, antioxidant	Scurvy, oxidative stress, weakness	[115, 116, 117]

Vitamin K

In 1936, vitamin K, as a key regulator of blood clotting was discovered. Limited evidence reveals the role of vitamin K in epigenetic phenomena. However, vitamin K is an integral part of two 75-kDa multimodular glycoproteins, namely protein S (ProS) and growth arrest-specific gene 6(Gas6) [154]. Similar to the other proteins dependent on vitamin k, ProS and Gas6 are needed for carboxylation reaction in glutamic acid residues to make them inactive [155]. About 40% of ProS is free in circulation and the rest of it is in a complex form with proteins [156]. In spite of the high expression of Gas6 in several tissues, such as vascular smooth muscle cells, bone marrow cells, and capillary endothelial cells, its concentration in circulation is much less than in ProS [157].

The role of ProS and Gas6 has been confirmed in the prevention of inflammation, angiogenesis, apoptosis, and, cancer [155, 158]. Induction of apoptosis is the main function of these two proteins. Immune cells especially macrophages cause clearance of apoptotic cells by interacting with a set of receptors, including Tyro3, Axl, and MerTK (TAM) tyrosine kinases [159, 160]. ProS and Gas6 are the main ligands of TAM receptors [156]. Only free ProS is able to induce TAM receptors. Dysfunction of TAM receptors results in the appearance of autoimmunity diseases and inflammatory responses. According to the studies, in control of lupus, cardiovascular diseases, and sepsis, accurate function of the Gas6-ProS-TAM system is important [161, 162, 163, 164, 165].

Epigenetic phenomena and water-soluble vitamins

Vitamin B2

Vitamin B2 or riboflavin mediates the one-carbon group metabolism required for S-adenosylmethionine reactions and histone function [47]. Vitamin B2 regulates modification of histone by activating lysine-specific demethylase 1 (LSD1) that is responsible for deleting methyl groups from the H3 element of histone. LSD1 removes mono and dimethyl groups by oxidative cleavage and reduces flavin in the form of 1,5-dihydroflavin adenine dinucleotide (FADH2) [166, 167]. The next step is related to the oxidation of FADH2 into FAD by the use of oxygen molecules. Indeed, the epigenetic effect of vitamin B2 is mediated by the function of LSD1 through redox reactions. However, overexpression of LSD1 downregulates expression of lysophosphatidylcholine acyltransferase 2(LPCAT2) and phospholipase 1 (PLD1) genes, which are involved in lipid metabolism [168, 169, 170].

Riboflavin in the FAD form induces Sir2 as a transcription regulator factor [170]. It has been found that vitamin B2 participates in the promoter regions of methylation of histone and a diet lacking vitamin B2 results in changing of methylation process [171]. Involvement of riboflavin in modification of epigenetic signature can be met by dietary intake of its daily recommended doses [98, 99].

Vitamin B3

Niacin in nicotinamide adenine dinucleotide (NAD^+) form mediates various pathways, such as redox reactions in cellular metabolism, cell signaling, activation of nucleotide syntheses, and folate-dependent enzymes [172, 173]. NAD^+ is considered a cofactor of NAD^+-dependent enzymes, including PARPs, SIRTs, and ADP-ribosyl transferase. Both calorie restriction and oxidative stress influence the activity of these enzymes by changing the NAD+/ nicotinamide adenine dinucleotide +hydrogen (NADH) ratio [97].

PARP enzymes activated by tryptophan amino acid and NAD+ are involved in cell differentiation, apoptosis, recombination, DNA repair, genome stability, and transcriptional activity [174]. The main role of PARP is the generation of poly ADP ribose sequences [175]. Other activities attributed to PARPs include protection against chronic genotoxic stress, maintaining genome integrity by protection of chromosome endpoints, and telomerase regulation [97].

SIRT as another NAD+-dependent enzyme contributes to deacetylation and ADP-ribosyltransferases activities that are needed for enzymatic reactions, transcription factors, histone levels, and co-regulation factors. Besides mitochondrial members of the SIRTs, non-mitochondrial members, including SIRT1, SIRT2, SIRT6, and SIRT7 exert the main roles in genome stability, cell survival, and apoptosis via regulation of gene expression of proteins, such as p53, NF-kB, hypoxia-inducible factor 1-alpha (HIF1a), and FOXO proteins. These proteins regulate epigenetic pathways via modulation of acetylated histone H4 lysine 16 (H4K16ac), acetylated histone H3 lysine 9 and 18(H3K9ac and H3K18ac), and chromatin-associated enzyme activities. SIRTs also interact with PGC1-α and PPARγ as key transcription factors. Other SIRTs involved in genome integrity are SIRT1, SIRT6, and SIRT7 contributing to DNA repair, genome structure, and organization, and SIRT2 contributing to regulation of the cell cycle [97]. Besides the development of pellagra, niacin deficiency influences various aspects about the integrity of epigenetic phenomena [172]. Deficiency of vitamin B3 exposes DNA to fragility and damage and increases the risk of sister chromatid exchanges and in contrast, supplementation of niacin attenuates genomic instability [175].

Similar to most vitamins, excessive levels of nicotinamide are accompanied by detrimental effects on

biological processes, such as DNAm. It has been reported that excess nicotinamide is degraded mainly through S-adenosylmethionine-dependent methylation catalyzed by nicotinamide N-methyltransferase and this interferes with DNAm reactions [176]. This effect leads to insulin resistance as one of the potential main causes of type-2 diabetes and obesity [176]. The DRI of niacin is mentioned as 2–18 mg/day, based on gender and age, and supplying by dietary foods seems to be logical and safe [98].

Vitamin B6

Vitamin B6 acts as a cofactor of the serine hydroxymethyltransferase (SHMT) enzyme used for producing 5,10-methylene THF from THF. The betaine homocysteine methyltransferase (BHMT) is another vitamin B6-dependent enzyme regulating the reaction of transferring methyl groups to homocysteine from methionine and the formation of dimethylglycine from betaine [177].

Considering the crucial role of vitamin B6 as a cofactor of enzymes involved in S-adenosyl-methionine (SAM) production, its deficiency influences the epigenetic pattern of the genome through methylation pathway [178]. Besides DNA hypomethylation, deficiency of vitamin B6 is manifested as the increase in chromosome breakage and impairment of DNA excision repair through decreasing levels of thymidine in DNA structure [179, 180]. Excess intake of vitamin B6 leads to overfeeding and obesity mediated by activation of dopaminergic pathways and PPAR-γ receptors [181].

Vitamin B9

The name of folate comes from the Latin word ″folium″ that means leaf [182]. Folate plays a key role in the one-carbon group's metabolism and methionine synthesis, and the synthesis of methionine plays a major role in one-carbon metabolism [183]. The main function of folate is attributed to cell division's activities, such as synthesis, expression, and repair of DNA [184]. 5-mTHF, as a coenzyme form of folate, provides methyl donors for all methyltransferases enzymes, for example, hydroxy indole-O-methyltransferase, catechol-O-methyltransferase, and phenylethanolamine-N-methyltransferase [103]. The N-5,10 mTHF is the metabolically active form of folate produced through conversion of serine into glycine during insertion of a methylene group from tetrahydrofolate. N-5,10 mTHF acts as a rate-limiting coenzyme in the synthesis of DNA precursors [172].

The epigenetic effect of folate is related to its involvement in DNAm, chromatin remodeling, modulating of micro-RNAs, and post-translational modification of histone proteins [35]. Methylation of CpG-dinucleotide is important in the regulation of cell growth, differentiation, cell division, and transcription pathways [185]. The normal pattern of DNAm plays a fundamental role in DNA integrity and cellular homeostasis [183].

DNA hypomethylation due to folate deficiency in all regions of DNA and specific genes involved in genome stability, such as p53 is associated with mutation, DNA breakage, and inactivation of DNA repair and tumor suppressor genes [183, 186], and results in the appearance of serious neurological, cardiovascular, and cerebrovascular abnormalities and cancers [187, 188, 189, 190]. Telomere sequences at the end of the chromosome preserve the genome from damage and degradation. Besides providing one-carbon groups to protect DNA, folate prevents the shortening of telomere. Shorter telomeres are associated with inflammation, the appearance of chronic diseases, and aging [191].

However, excess intakes of dietary folate similar to other methyl donors alter methylation patterns and result in hypermethylation of basic genes [181]. For example, a higher amount of folic acid may worsen methionine synthesis under vitamin B12 deficiency conditions, change the availability of SAM in reactions, and decrease methylation levels [192].

Vitamin 12

Vitamin B12 and its related derivatives exert many biological functions in the body. Also, vitamin B12 contributes to brain development by providing one-carbon molecules required for the formation of SAM in trans-methylation pathways [193]. Moreover, vitamin B12 is involved in various functions of synthesis, repair, and expression of DNA. Any deficiency in vitamin B12 in the diet leads to the breakdown of DNA strand, departure in chromosomes, and DNA replication stress [194]. Vitamin B12 deficiency not only is involved in carcinogenesis in tissues via decreasing methylation and increasing uracil-dependent reaction but also results in an abnormality of cholesterol metabolism through influencing the expression of the related genes, including low-density lipoprotein receptor(LDLR) and sterol regulatory element-binding protein-1(SREBF1) [195]. In adults, intake of 2.4 μg of vitamin B12 provides the daily requirement of vitamin B12, and especially its supplementation is suggested in at-risk groups e.g., vegans [196, 197].

Vitamin C

Vitamin C is an essential nutrient for humans and primates. Despite humans, other mammals have the ability to synthesize this vitamin from glucose. Besides the development of scurvy, a diet lacking vitamin C can result in disturbance of epigenetic patterns and incidence of the related diseases, such as cancer and neurodegenerative disorders [198].

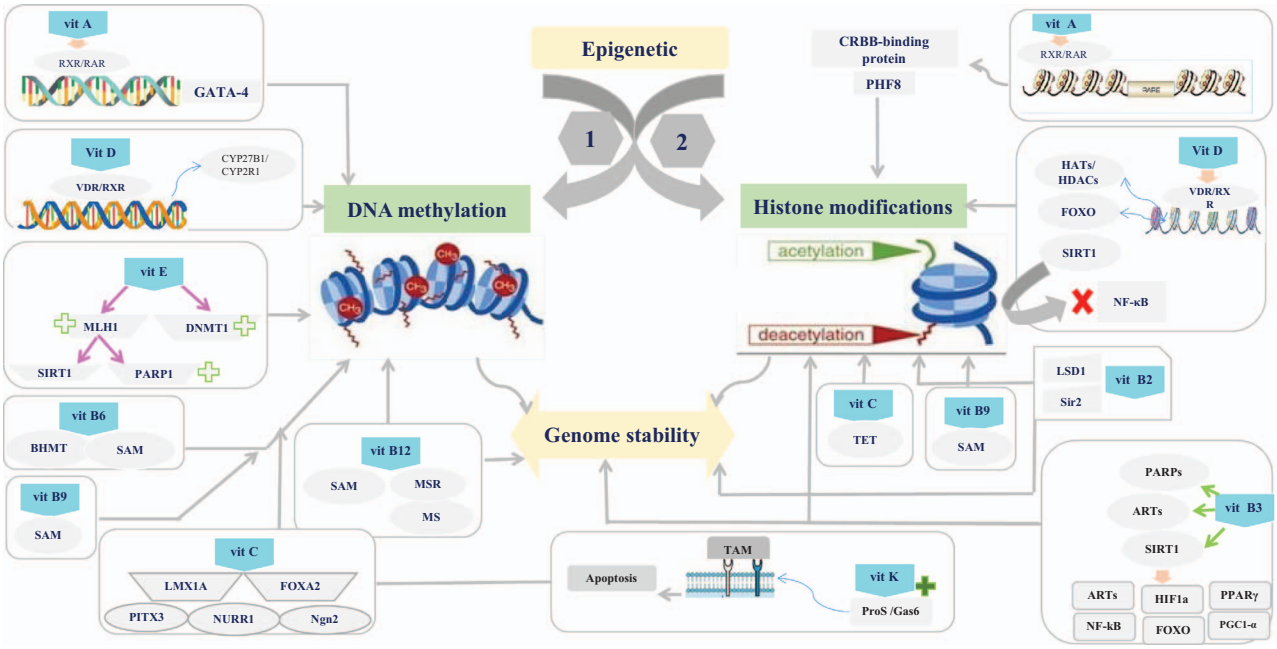

Figure 2. The interaction between soluble and insoluble vitamins and epigenetic pathways. RXR/RAR: Retinoid X receptors/retinoic acid receptors; GATA-4: GATA-binding protein 4; CYP2R1: Cytochrome P450 family 2 subfamily R member 1; CYP27B1: cytochrome P450 family 27 subfamily B member 1; MLH1: MutL homolog 1; DNMT1: DNA methyltransferase 1; SIRT1: Sirtuin 1; PARP1: Poly (ADP-ribose) polymerase 1; BHMT: Betaine-homocysteine methyltransferases; SAM: S-adenosyl-methionine; LMX1A: LIM Homeobox transcription factor 1 alpha; PITX3: Paired like homeodomain 3; Nurr1: Nuclear receptor related 1; Ngn2: Neurogenin 2; MS: Methionine synthase; MSR: Methionine synthase reductase; TAM: Tyro3, Axl, MerTK; ProS: Protein S; Gas6: Growth arrest-specific; TET: Ten-eleven-translocation; CREB proteins: cAMP-response element binding proteins; PHF8: PHD finger protein 8; HATs: histone acetyltransferases; HDACs: Histone deacetyltransferase; FOXO proteins: Forkhead box O proteins; NF-kB: Nuclear factor-kB; LSD1: lysine-specific demethylase 1; ARTs: ADP-ribosyltransferase; HIF1a: Hypoxia-inducible factor 1a; PGC1-α: Peroxisome proliferator gamma coactivator 1-α.

Vitamin C as a cofactor of demethylation of histone and DNA breakdown enzymes acts in the regulation of epigenetic phenomena. The role of vitamin C in DNAm is mediated through activation of TET hydroxylase enzymes [199, 200, 201]. The highest level of vitamin C is found in the brain especially during embryonic development [202].

Vitamin C increases upregulation of FOXA2 and LIM homeobox transcription factor 1 alpha(LMX1A) markers during differentiation of neurons by enhancing expression of the related genes, including nuclear receptor-related 1 protein(NURR1), pituitary homeobox 3(PITX3), and neurogenin 2 (Ngn2) [202, 203, 204] and improves defect in neurons as etiological causes of degenerative brain diseases [116]. Indeed, vitamin C increases the mRNA level of these markers during the transcription stage.

In addition, vitamin C acts as a cofactor of $Fe2^{+}$-oxoglutarate-dependent dioxygenase enzymes (ten-eleven-translocation) and Jumonji (JmjC)-domain-containing enzymes in the demethylation of lysine residues of histone proteins [205]. Enough concentration of vitamin C is needed to maintain the activity of histone H3 acetylation and Lys4 methylation [206].

There is a significant correlation between up-regulation of TET enzymes and high levels of 5-hydroxymethylcytosine in CpG sites of the promoter region [116]. It has been shown that TET1 and TET2 activities are displayed in DNAm patterns and enhance reprogramming efficiency [207, 208]. Other proteins activated by vitamin C include the AlkB family, which is involved in DNA and RNA repairing [206, 207]. AlkB and its mammalian homologs, ABH2 and ABH3 mediate DNA repair by oxidation of 3-methylcytosine and 1-methyladenine [209]. Vitamin C also modulates the metabolism of bone and cartilage via various mechanisms, such as upregulation of osterix (Osx) by causing nuclear respiratory factor 1 (Nrf1) to bind to an antioxidant-responsive element (ARE) in the Osx promoter [210], enhances bone formation, and prevents bone fracture via acting as a cofactor of prolyl hydroxylase domain protein 2 (PHD2) [211]. Figure 2 summarizes the interaction between soluble and insoluble vitamins and epigenetic pathways.

Future perspectives

Given the role of epigenetic disturbance in the incidence of NCDs and the obvious role of vitamins and dietary patterns in epigenetic pathways, designing future studies is recommended to determine the dietary patterns of patients with

NCDs and to clarify the disrupted epigenetic pathway in these patients. Moreover, conducting further studies is suggested to identify the other unknown mechanisms influencing the interaction between nutrients and epigenetic pathways.

Conclusion

In this review paper, the role of vitamins and dietary patterns in the epigenetic aspect of NCDs, the mechanisms of action of vitamins in epigenetic modification, and the effects of vitamins deficiency on changes of the epigenetic pattern were described. Indeed, presenting a holistic perspective about the role of nutrients in epigenetic modification can be considered as the novelty and strength of this paper. Considering strong evidence about the crucial role of a healthy diet in providing daily requirements of vitamins, it is necessary to be familiar with dietary sources of soluble and insoluble vitamins and components of healthy dietary patterns, such as the DASH (dietary approaches to stop hypertension) and Mediterranean diets and avoiding the western diet components. Adherence to an approved healthy dietary habit during life-span is also recommended.

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