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Review

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Epigenetic and nutrigenetic aspects of vitamin C in clinical practice including pregnancy

Epigenetyka i nutrigenetyka witaminy C, implikacje kliniczne z uwzględnieniem okresu ciąży

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Summary

Vitamin C, first described over 90 years ago, is still being discovered by scientists today. Current epigenetic, nutrigenetic, and nutrigenomic research has given us a new understanding on why vitamin C is essential for optimal health at every stage of life. Ascorbic acid is involved in epigenetic reprogramming as an indispensable enzymatic cofactor in DNA demethylation in early preimplantation of embryos in utero, a process regulating fetal growth and development. Another role of vitamin C in pregnancy is associated with genetic variants in sodium-dependent vitamin C transporters (SVCT) that may be connected with spontaneous preterm birth as a result of premature membrane rupture. Vitamin C, as an exogenous antioxidant supports an endogenous, internal antioxidant system and protects against damage to DNA and cell membranes, especially against lipid peroxidation in tissues like brain or reproductive cells. Currently, ascorbic acid is believed to be a neuromodulator of glutamatergic, dopaminergic, and GABAergic transmission pointing to its role as a modulator of human behavior. Genetic variants of vitamin C transporters are considered to be one of many possible predisposing factors associated with Chronic Non-Communicable Diseases (NCDs) such as cancer, cardiovascular disease, osteoporosis, or neurodegenerative diseases (all are characterized by a significant overproduction of free radicals). The most efficient in protection against free-radical damage to DNA are fresh vegetables and fruits containing ascorbic acid, as advised by WHO and FAO (FAO/WHO 2004). Consuming 5 servings of fresh and cold vegetables and fruits daily allows for a constant supply of vitamin C and prevents its deficiency.

Keywords: **Ascorbic Acid • Vitamin C Transporters • Epigenetics • Nutrigenetics • Nutrigenomics • Pregnancy**

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Abbreviations: **2-KG** – 2-ketoglutaric acid, **5-caC** – 5-carboxycytosine, **5-fC** – 5-formylocytosine, **5-hmC** – 5-hydroxymethylcytosine, **5-hmU** – 5-hydroxymethyluracil, **5-mC** – 5-methylcytosine; **AA** – Ascorbic Acid, **DHA** – Dehydroascorbic Acid, **DNMT** – DNA methyltransferase, **EAR** – Estimated Average Requirements, **GLUT** – Glucose Transporter, **HIF-1α** – HypoxiaInducible Factor α, **MD** – Mean Difference, **NCDs** – Chronic Non-Communicable Diseases, **PROM** – Prelabour Rupture of Membranes, **RDA** – Recommended Dietary Allowance, **ROS** – Reactive Oxygen Species, **RR** – Risk Ratio, **SAH** – S-adenosylhomocysteine, **SAM** – S-adenosylmethionine, **SVCT** – Sodium dependent Vitamin C Transporter, **SLC** – Solute Carrier, **SNP** – Single Nucleotide Polymorphism, **TDG** – DNA glycosylase, **TET** – Ten-eleven translocation enzymes (proteins involved in active DNA demethylation).

INTRODUCTION

The dynamic development of genetic research over the last several decades and the completion of the Human Genome Project in 2003 has led us to understand that it is not enough to know the structure of DNA, chromosomes, nor the whole genome to explore human genetic mysteries [48]. Two genetically identical individuals or two genetically identical animals may develop extremely different phenotypes and fall ill from other diseases if exposed to different environments or stimuli (a lesson learned from the agouti mice model) [31]. The beginning of the third millennium unveiled a new area of scientific research on the regulation of gene function. Not only the structure of a gene, but also its expression or silencing thereof in response to endogenous or exogenous stimuli contribute to a full "dynamic" image of the gene [16]. The science that explores gene expression regulation is *epigenetics*. Genes are DNA fragments containing information on the structure, i.e. the quality and amount of amino acids of one polypeptide chain of a particular protein. The DNA regulatory sections do not code for proteins, but they determine the amount of individual proteins. Environmental factors contribute to the modulation of information contained in DNA. Non-genetic factors (food ingredients, physical activity, sleep, stress, oxygen in environment, etc.) involved in gene interactions are considered as the epigenome [12, 56]. Natural bioactive food components affect gene expression through various mechanisms with the field of science dealing with the study of these phenomena being *nutrigenomics* (Figure 1) [5]. Simply put, nutrigenomics examines how nutritional factors protect the genome from damage. On the other hand, the inter-individual variability of genes involved in the metabolism of nutrients is responsible for inter-individual differences in responses to dietary components [34, 44, 55]. The effects of genetic variation on a body's response to a diet (genotype determines the response to food) is dealt with by *nutrigenetics* (Fig. 1) [61]

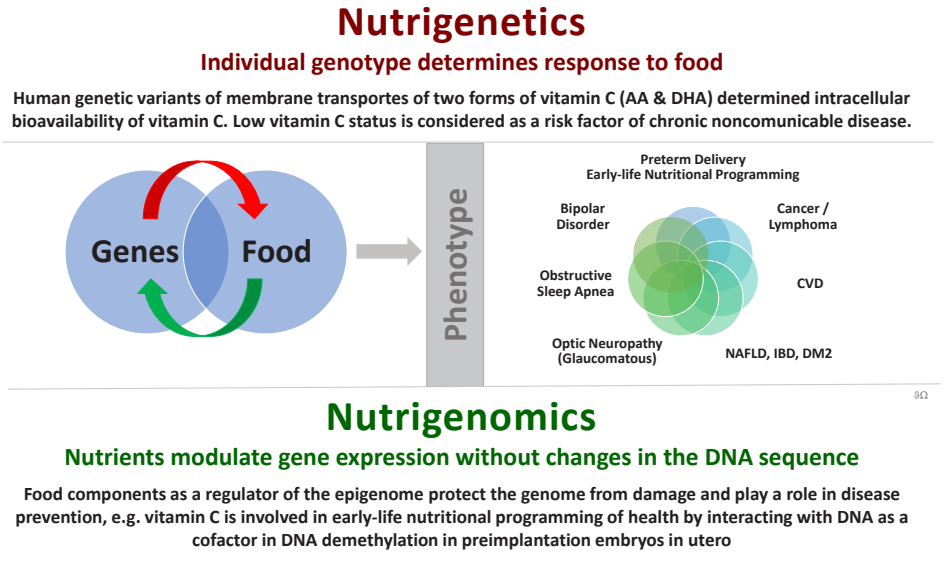

Fig. 1. Potential clinical phenotypes resulting from nutrigenetic and nutrigenomic interactions, illustrated by the example of vitamin C. AA - Ascorbic Acid, DHA - Dehydroasorbic Acid, CVD - Cardiovascular Diseases, NAFLD - Nonalcoholic Fatty Liver Disease, IBD - Inflammatory Bowel Diseases, DM2 – Type 2 Diabetes Melitus

Nutrigenetics and nutrigenomics are the basis of modern personalized nutrition, a key component in personalized medicine [90]. With the development of nutrigenetics and nutrigenomics, the era of a generic healthy diet suitable for everyone has passed. Our genes determine what we should eat to enjoy a healthy and long life. In developing a menu tailored to the needs of a specific person (a personalized diet), important information is provided by individual gene variations known as single nucleotide polymorphisms (SNPs). SNPs may have no clinical relevance or may alter gene function and predispose to health problems, depending on the genetic and environmental context. SNPs concerning genes encoding for important enzymes involved in various overlapping metabolic pathways may predispose to chronic health problems such as autoimmunity, allergy, cancer, and neuropsychiatric or cardiovascular disorders [12, 41, 82]. Inter-individual variability of genetic variants (SNPs) affecting the quantity and quality of proteins related to the action and metabolism of food components (i.e. macronutrients, micronutrients, and vitamins such as A,B, C, D, E) can increase or decrease the risk of certain chronic diseases affecting various organs [34, 57]. In this paper we summarize available clinical knowledge based on current nutritional science, including epigenetics and nutrigenetics, of vitamin C's action on the human organism as well as pregnancy.

CHEMISTRY AND METABOLISM OF VITAMIN C

Vitamin C (ascorbic acid, $C_6H_8O_6$), a 6-carbon lactone, is the poly-alcohol-acid oxidation product of polyalcohol-aldehyde (glucose-$C_6H_{12}O_6$) and is soluble in water due to the presence of alcohol groups forming hydrogen bonds with water (Figure 2).

Humans lost the ability to synthesize vitamin C from glucose (for the oxidation of aldehyde glucose) following the mutation of the gene responsible for the synthesis of the L-gulono-γ-lactone enzyme (GULO) (EC1.1.3.8) more than 40 million years ago [24]. For humans, vitamin C auxotrophs, just as for primates, guinea pigs and some species of bats, ascorbic acid is a vitamin (an exogenous nutrient), a chemical compound necessary for proper functioning and must be supplied with food [70].

Vitamin C was isolated for the first time in 1928 from bovine adrenal cortex, orange juice, as well as from paprika by Hungarian biochemist and Nobel Prize winner A. Szent-Györgyiand and was later synthesized in 1932 by Walter Norman Haworth [3]. Ascorbic acid is unstable and under the influence of external factors (light, moisture, elevated temperature, oxygen, metal ions, alkaline environment, etc.) is easily converted into biologically inactive components such as 2,3-dioxo-L-gulonic acid, oxalic acid, L-threonic acid, and L-xylonic acid [59]. Strong reducing properties of vitamin C contained in foods decrease, for example, under the influence of heat (i.e. cooking, frying, pasteurization, convection drying, thawing at high temperatures) and exposure to sunlight that easily oxidizes vitamin C. Therefore, the best source of active (reduced) vitamin C is fresh and unprocessed vegetables and fruits eaten cold. Naturally derived vitamin C is 3-5 times more active than synthetic derivatives and its co-occurrence in plant food compounds such as bioflavonoids or phenol acids enhances its effects. Cooking vegetables in water is preferably replaced by steaming. The main sources of natural vitamin C are vegetables (mainly green), such as broccoli, spinach, peas, cauliflower, peppers, tomatoes, and fruits both tropical (i.e. citruses) and temperate (i.e. strawberries, currants) [50]. L-ascorbic acid is a functional form of vitamin C, where three other stereoisomers (D-ascorbic acid, D-isoascorbic acid, and L-isoascorbic acid) do not have the same anticorrosive properties. L-ascorbic acid has strong reducing properties and is oxidized to L-dehydroascorbic acid (DHA) [70].

FUNCTIONS OF VITAMIN C

The pleiotropic effect of vitamin C is essential for many physiological functions in the body, such as mitigating the consequences of oxidative stress and regulating the function of many enzymes for which vitamin C is an essential cofactor, which is why it is crucial to maintain adequate concentrations of vitamin C in plasma and tissues. This is especially true for hydroxylases, Cu(+)-dependent monooxygenases, and Fe(2+)-dependent dioxygenases(including the ten-eleven translocation [TET] enzyme family involved in DNA

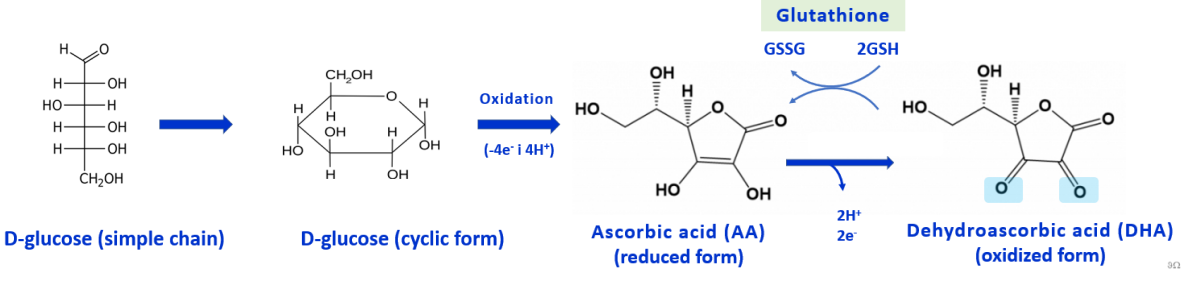

Fig. 2. Ascorbic acid formation from the D-glucose chain and its recycling: oxidation reaction of ascorbic acid to dehydroascorbic acid. Dehydroascorbic acid can be reduced to ascorbic acid by glutathione (GSH), GSSG - Glutathione Disulfide, oxidized form of glutathione

demethylation) [70, 98]. Vitamin C plays a key role, among others, as a cofactor in the synthesis of neurotransmitters (conversion of dopamine into noradrenaline by dopamine-ß-monooxygenase, synthesis of serotonin from tryptophan by tryptophan-5-hydroxylase), in hormone synthesis (oxidation of tyrosine, hydroxylation of cortisol), synthesis of fatty acids (cholesterol hydroxylation by 7α-hydroxylase), in structural components of the skin, bones, cartilage, teeth, cornea and eye lenses, ligaments, heart valves, blood vessels, and intervertebral discs. Furthermore, vitamin C plays a role in the absorption of non-heme and heme iron in the stomach, conversion of folic acid to folinic acid (play a role in the prevention of iron-deficiency anaemia and megaloblastic anaemia), detoxification of exogenous substances, and affects cytochrome P450 activity [47, 69, 70, 85]. An important function of vitamin C is seen in collagen biosynthesis through participation in the hydroxylation of proline residues and transformation of lysine into hydroxyproline and hydroxylysine. It is also an indispensable cofactor of enzymes involved in the synthesis of carnitine from lysine and methionine [58]. In vitamin C deficiency, the urinary loss of carnitine increases, which may be accompanied by accumulation of serum triacylglycerols and is characteristic for scurvy fatigue [85]. Ascorbic acid is involved in histamine metabolism, acting with Cu2+ to inhibit its release and enhance its degradation [54].

Ascorbic acid is an important water-soluble antioxidant for most cells of the human body, which means that it protects cells from reactive oxygen species (ROS). ROS have been implicated in more than 100 diseases. Vitamin C contributes up to 30% of the 'total antioxidant power' of plasma [7]. The antioxidant properties of ascorbic acid make it an effective scavenger of free radicals (FRS): superoxide anions (O_2^-), singlet oxygens ($^1O_2$), hydroxyl radicals (OH •) and prevent the oxidative damage of lipids, proteins, and DNA [40, 81, 83, 84]. The principal producer of ROS is the mitochondrial respiratory chain, primarily in the forms of O_2^- and H_2O_2. Vitamin C is not, however, an effective scavenger or neutralizer of hydrogen peroxide (H_2O_2) [65]. Under certain conditions vitamin C can act pro-oxidatively, for example in connection with metals such as iron or mixed with N-acetyl-cysteine [18]. Vitamin C reacts not only with ROS but also with reactive nitrogen species (RNS) (nitric oxide NO, nitrogen dioxide NO_2) [25]. Ascorbic acid also has significant interactions with a number of other antioxidants. Glutathione is important in recycling oxidized vitamin C (Fig. 2), and vitamin C itself is crucial to the regeneration of lipid-soluble and membrane-bound vitamin E. Ascorbic acid can reduce the free tocopherol radical to tocopherol, protects Fe2+ from oxidation to Fe3+, prevents the oxidation of -SH groups contained in the cysteinyl residues of proteins, and reduces ROS [83].

A particularly important function of vitamin C is protection against lipid peroxidation; it has a protective function related to the shielding effect of vitamin E on membrane phospholipids [81]. During the oxidation of unsaturated fatty acids, proteins, and DNA chains, specific peroxidation products arise that can be measured by laboratory methods [84]. Tissues particularly susceptible to oxidative stress are those containing large amounts of polyunsaturated fatty acids, i.e. brain and reproductive cells. Increased oxidative stress and redox imbalance are one of the recognized pathomechanisms of infertility with antioxidants being used in adjuvant treatment of infertility through protection against DNA fragmentation. In cases of male infertility, increased levels of free radicals correlate with decreased sperm motility rates and vitamin C supplementation in infertile men may improve sperm count, motility, and morphology [3].

Vitamin C is involved in the response to hypoxia as a cofactor of hydrolases involved in the regulation of HIF-1α protein stability, (Hypoxia-Inducible Factor 1-α) [40, 66]. HIF-1α as a transcription factor participates in the activation of over 100 genes that allow cells to adapt to a reduced oxygen concentration through expression of the glycolysis pathway, erythropoiesis stimulation, increased respiratory rate, and vascular system control. The accumulation of HIF-1α in tumor tissue is inversely correlated with the survival time of patients, which prompted research into the effectiveness of adding intravenous ascorbic acid to chemotherapy [38]. The anti-cancer role of vitamin C is evidenced by research on the mucous membranes of the stomach. Ascorbic acid serves a protective function here against free radicals and prevents the formation of carcinogenic nitrosamines from nitrate (III) in the stomach and nitrate (V) contained in the diet [32]. High citrus intake and high levels of vitamin C also reduce the risk of cancer in the stomach by affecting Helicobacter pylori infection [32]. Very high doses of vitamin C may inhibit the development of H. pylori infection by inhibiting bacterial growth and reducing the risk of reinfection [117].

VITAMIN C PHYSIOLOGY IN HUMANS

Total body stores of ascorbic acid have been estimated to be about 1.5 g with about a 30 to 45 mg daily turnover. Plasma concentrations of ascorbic acid can rise up to 90 mg daily. Distribution of vitamin C in the body is uneven with the highest concentration of ascorbate occurring in the brain (necessary for neuronal maturation and antioxidant defense due to high neuronal mitochondrial metabolism) and in neuroendocrine tissues (i.e. adrenal glands), where ascorbic acid acts as a modulator of glutamatergic, dopaminergic, and GABAergic neurotransmission [47].

Vitamin C requirements depend on age and gender and vary depending on a person's physiological condition (physical effort, pregnancy, breastfeeding, old age), coexisting diseases (diabetes, infections, injuries, cancer), and any exposures to factors both physical and chemical (alcohol, tobacco smoke, UV radiation, drugs [contraceptives, acetylsalicylic acid]) [68]. The recommended daily allowance (RDA) is about 90-100 mg/day for an

adult male, 75 mg/day for an adult female while increasing during pregnancy and lactation to 80-120 day [50, 92]. Regardless of gender, the daily requirement for vitamin C increases by 35 mg in smokers. The average daily dose of approximately 100 mg of natural ascorbate from vegetables and fruits provides a concentration of vitamin C in the plasma not exceeding 100 μmol/L [67]. Peak plasma vitamin C concentrations are achieved approximately 120-180 minutes after ingestion. With increasing oral doses of vitamin C, its bioavailability decreases and after reaching a plateau the plasma concentration does not usually exceed 250 μmol/L. Therefore, increasing the dose of oral vitamin C does not translate into an increase in its concentration in plasma. An excess of unchanged ascorbic acid, similar to inactive ascorbic acid metabolites, is excreted in the urine. The pharmacokinetics of intravenous vitamin C differ slightly. Pharmacological ascorbate concentrations of 25-30 mmol/L can be safely achieved with intravenous infusions of vitamin C [8, 67].

Vitamin C deficiency is defined as a plasma concentration below 11 μmol/L (below 0.2 mg/dL). The lower limit is defined as a plasma vitamin concentration between 11 and 28 μmol/L [53]. Average concentrations of vitamin C range 50-100 μmol/L, 95% of which is reduced ascorbic acid, while the remaining 5% is the oxidized form - dehydroascorbic acid [59]. The ratio of dehydroascorbic acid to ascorbic acid (DHA/AA) in plasma is viewed as a marker of oxidative stress [72]. High-performance liquid chromatography can evaluate both reduced ascorbic acid and oxidized dehydroascorbic acid levels.

The consequence of chronic vitamin C deficiency is scurvy. In the past, the victims of scurvy were, for example, sailors exposed for many months to a lack of fresh vegetables and fruits or residents of northern Europe during cold winters. Symptoms of scurvy develop after 1-3 months of a complete lack of dietary vitamin C and include bleeding from the nose and gums, ecchymoses, follicular hyperkeratosis, dry skin, dryness of the conjunctiva and mucous membranes of the mouth, atrophy of the gums, loss of teeth, anemia, impaired wound healing, limb edema, stiff joints, painful muscles and degeneration of bone and cartilage [15, 84]. Vitamin C deficiency is still quite common, being diagnosed in 5-10% of the population in industrialized countries and presents with milder symptoms. Low plasma levels of vitamin C are commonly associated with chronic diseases presenting with long lasting oxidative stress (nicotinism, alcoholism, type I diabetes, cataracts, cancer, osteoporosis, systemic lupus, AIDS) [25, 68, 69, 84, 98].

VITAMIN C TRANSPORTERS

The body's cellular supply of vitamin C depends on the quantity of vitamin C intake and also on factors such as the presence and severity of oxidative stress, coexistence of inflammation, or the activity of transmembrane transporters [13, 95]. In addition to variations in vitamin C transporters, Haptoglobin (HP) and Glutathione S-Transferase (GST) gene variants have also been associated with serum ascorbic acid concentrations and may explain the high inter-individual variability of circulating vitamin C concentrations [24]. GSTs area family of phase II detoxifying enzymes that contribute to the glutathione-ascorbic acid antioxidant cycle. Three GST isoforms are coded by the *GSTM1*, *GSTT1*/*GSTT2,* and *GSTP1* genes. Null genotypes of GST isoforms may increase the risk of vitamin C deficiency 4-12 fold in subjects who do not meet the recommended dietary allowance [24]. Haptoglobin is a hemoglobin-binding antioxidant controlling free hemoglobin oxidative reactions when released from red blood cells (in conditions such as hemolyticanemia, thalassemia, paroxysmal nocturnal hemoglobinuria (PNH), drug-induced hemolyticanemia, and certain enzymopathies). Haptoglobin is genetically determined by two autosomal codominant allelic genes, *Hp 1* and *Hp 2*, and displays genetic polymorphism with three possible genotypes *Hp 1-1, Hp 2-1,* and *Hp 2-2.* The *Hp 2-2* genotype has been associated with lower vitamin C serum concentrations and with an increased risk of atherosclerosis [14].

Inter-individual variability of vitamin C concentration is also explained by different genetic variants and genes responsible for the transport of ascorbic acid in the body [13]. The intracellular concentration of ascorbic acid is regulated by means of two mechanisms: 1) active transport of ascorbic acid with SVCT transporters (Sodium-dependent Vitamin C Transporters), encoded by sodium dependent *SLC* genes (*SLC* solute carrier family); 2) transporting DHA, with the participation of membrane transporters belonging to the GLUT family responsible for the facilitated transport of glucose. DHA is immediately reduced to ascorbate inside the cell (Fig. 3) [98, 106, 112].

The transmembrane pathways of the active sodium-dependent transport of ascorbic acid consist of two SVCT1 and SVCT2 transporters which are encoded by the *SLC23A1* (OMIM 603790) and *SLC23A2* (OMIM 603791) genes, respectively [13]. Genetic variants of the SVCT1 and SVCT2 transporters modulate the effects of consumed vitamin C on serum vitamin C concentration [13]. The *SLC23A1* and *SLC23A2* genes were cloned for the first time in 1999 [106]. The SVCT1 and SVCT2 transporters, operating as pumps and requiring energy in the form of ATP, cause the concentration of vitamin C inside the cell to be 50 times higher than in the intercellular fluid, which is responsible for the electrochemical gradient of Na+ ions. Pumps requiring energy in the form of ATP move sodium cations (Na+) outside the cell via the cell membrane. On the outside of the cell, a higher concentration of Na + cations is formed than inside the cell. Using the electrochemical gradient of Na+ cations vitamin C molecules enter the cells. This phenomenon is called cotransport by symporters.

Vitamin C transporters provide the optimal concentration of vitamin C in all cells of the body (except for erythrocytes) and extracellular fluid. The tissue-specific expression of the vitamin C transporter genes

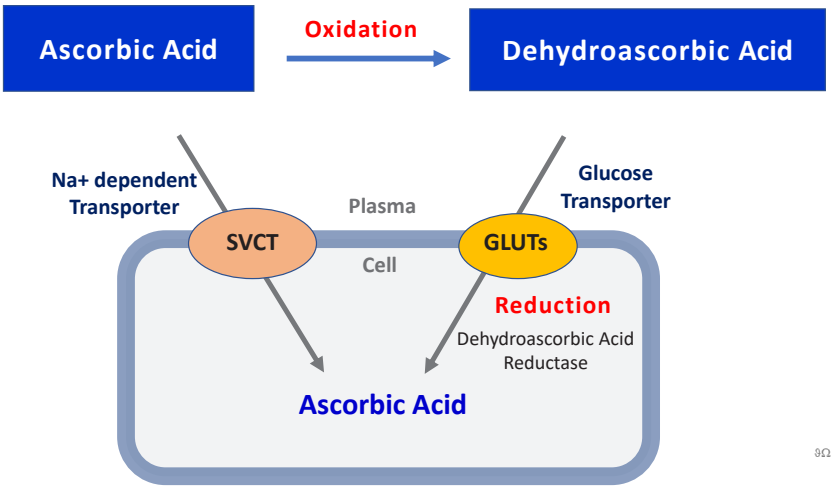

Fig. 3. Transmembrane transporters of ascorbic acid and dehydroascorbic acid: Sodium - dependent Vitamin C Transporters (SVCT) are specific for ascorbic acid, and Glucose Transporters (GLUTs) are specific for dehydroascorbic acid

results from the various functions of vitamin C in the metabolism of specific organs. The SLC23A1 transporter is responsible for the active transport of ascorbate to the epithelial cells in the gastrointestinal tract (SLC23A1 is more active in the small than the large intestine) and the reabsorption of vitamin C in kidney tubules [27, 95, 105]. SLC23A2 protein expression occurs in most human tissues (except lungs and skeletal muscles) (Table 1). It is believed that the SLC23A2 transporter regulates the intracellular concentration of ascorbate that provides the cell with protection against oxidative stress. SVCT2 is the only transporter of ascorbic acid in articular cartilage and a lowering of *SLC23A2* gene expression is found in arthritis [9].

Very unstable dehydroascorbic acid, with a half-life in the blood about 2-6 minutes, is absorbed by the brush border of the intestinal epithelium, and after entry into the enterocyte, is reduced to ascorbate. Reduction of DHA to AA leads to a decrease in DHA concentration inside the enterocyte, favoring further DHA absorption to restore its proper concentration [22, 112]. DHA transporters are involved in transmembrane dehydroascorbate transport, which also mediates glucose uptake in the cell. This is reminiscent of the biological and structural relationship to glucose: ascorbic acid is a product of glucose oxidation and DHA is the product of AA oxidation. The GLUT family of transporters consists of 14 proteins which participate in the transport of sugars with some participating in the transport of dehydroascorbic acid (DHA-GLUT transporters): GLUT1 (SLC2A1), GLUT2 (SLC2A2), GLUT3 (SLC2A3), GLUT4 (SLC2A4), GLUT8 (SLC2A8), GLUT14 (SLC2A14) (Table 2) [99]. DHA diffusion into certain cells may be impeded during a high-glucose state by the lack of access to SLC2A transporters.

CLINICAL SIGNIFICANCE OF SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) IN VITAMIN C TRANSPORTER GENES

Human vitamin C transporter gene variations (SNPs) may be linked with plasma, cell, and tissue vitamin C status and consequently be associated with a risk or reduction in the risk of common chronic diseases. The clinical significance of gene polymorphisms in *SLC23A1* and in *SLC23A2*have not yet been fully described, however, research is ongoing in various fields of medicine. At present, SNP *SLC23A2*seems to be associated with more conditions than *SLC23A1*, including cancer, cardiovascular diseases, optic neuropathy, or inflammatory bowel disease (Table 1) [79, 98].

ONCOLOGY. Relevant *SLC23A2* polymorphisms are associated with a risk of developing cancers affecting the esophagus, stomach, large intestine, bladder and urinary tract, as well as the head and neck [2, 17, 32, 36, 70, 79, 113]. The antioxidant effects of vitamin C may prevent cancers by inducing apoptosis, suppressing tumor cell growth, and inhibiting *N*-nitroso compound formation in the stomach [98]. Gastric cancer risk was inversely associated with one of 13 studied SNPs (rs12479919) in the *SLC23A2* gene (AA homozygotes had a 41% lower gastric cancer risk than GG homozygotes, 279 cases/414 controls; Poland) [113]. In another study four SNPs (in both*SLC23A1* and *SLC23A2* genes) were associated with plasma vitamin C levels and one *SLC23A2* marker (rs6116569, intronic) was associated with non-cardiac gastric cancer, 365 cases/1284 controls; 10 European countries; additionally over 80% of gastric cancer cases were positive for H. pylori infection [32]. A high-risk genotype for a gene-gene effect on bladder cancer was found for variant rs12479919 CT in the*SLC23A2* gene (832 cases, high percentage of current smokers/1191 controls; USA) [2]. Certain researchers suggest that vitamin C uptake and storage are involved in lymphoma pathogen-

Table 1. Disease susceptibility resulting from genetic variation (SNPs) in Sodium-dependent Vitamin C Transporters (SVCT) genes (adapted from Shaghaghi 2016 [98])

Gene		Location and action of transporter	Associated conditions	SNP (Allele)	Risk (↑↓) genotype
SVCT1	SLC23A1 Chromosome 5q31.2	Epithelium of the small intestine, kidneys, skin, liver, and lungs. Responsible for intestinal absorption and reabsorption through the kidney and systemic homeostasis and maintaining the correct concentration of circulating vitamin C in the body	Follicular Lymphoma (FL)	rs11950646 (A/G)	↑ Risk GG genotype [103]
				rs6596473 (G/C)	↑ Risk CC genotype [103]
			Chronic lymphocytic leukemia	rs11950646 (A/G)	↑ Risk GG genotype [103]
				rs6596473 (G/C)	↑ Risk CC genotype [103]
			Diffuse large B-cell lymphoma	rs6596473 (G/C)	↓ Risk CC genotype [103]
			Inflammatory Bowel Disease (Crohn Disease)	rs10063949 (A/G)	↑ Crohn disease risk GG genotype [1] ↑ Crohn disease risk AG genotype
SVCT2	SLC23A2 Chromosome 20p13	Tissue uptake of vitamin C (eyes, brain, bones, heart, adrenal glands, skeletal muscles, placenta) Responsible for the antioxidative effect of ascorbic acid in particularly active metabolic tissues, e.g. brain, adrenal glands, eyes.	Non-Hodgkin lymphoma (NHL): Diffuse large B-cell lymphoma Small lymphocytic lymphoma	rs6133175 (A/G)	↑ Risk GG genotype [103]
				rs1715385 (G/A)	↑ Risk AA genotype [103]
				rs1715364 (T/C)	↑ Risk CC genotype [103]
			Diffuse large B-cell lymphoma	rs1715385 (G/A)	↑ Risk AA genotype [103]
			Follicular lymphoma	rs1776948 (G/A)	↑ Risk AA genotype [103]
			FL, Small lymphocytic lymphoma	rs1776948 (G/A)	↑ Risk AA genotype [103]
			Small lymphocytic lymphoma	rs6139587 (T/A)	↑ Risk AA genotype [103]
			Colorectal adenoma	rs4987219 (G/C)	↓ Risk C-carrier [36]
				rs1110277 (T/C)	↓ Risk C-carrier [36]
			Human papillomavirus, head and neck squamous cell carcinomas association	rs4987219 (G/C)	↑ Risk G-carrier [17]
			Esophageal squamous cell carcinoma	rs4987219 (G/C)	↑ Risk leukopenia C-carrier [79]
				rs1110277 (T/C)	↑ Risk stomatitis T-carrier [79]
			Gastric cancer	rs12479919(C/T)	↓ Risk TT genotype [113]
				rs6116569 (C/T)	↑ Risk T-carrier [32]
			Bladder cancer	rs12479919 C/T)	↑ Risk CT genotype [2]
			Lower concentration of ocular ascorbate	rs12479919 C/T)	↑ Risk TT genotype [97]
			Preterm delivery	rs2681116 (G/A)	↑ Risk GA genotype [35]
				rs6139591 (C/T)	↑ Risk T-carrier [35]
				rs1776964 (C/T)	↓ Risk TT genotype [35]
			Acute coronary syndrome	rs6139591 (C/T)	↑ Risk TT genotype [26]
				rs1776964 (C/T)	↑ Risk TT genotype [26]
			Primary open glaucoma	rs1279683 (A/G)	↑ Risk GG genotype [116]/EndNote>

esis. Several SNPs in SLC23A1 and SLC23A2 have been associated with an increased risk of non-Hodgkin lymphoma (SLC23A1 genotypes [rs6596473 CC and rs11950646 GG] showed an 80% elevated risk of lymphoma, 1292 cases/1375 controls; USA) [98, 103]. Certain *SLC23A2* transporter polymorphisms have been suggested as predictive biomarkers of oncological treatment and toxic response to chemoradiotherapy such as stomatitis and leukopenia in the course of esophageal carcinoma (rs4987219 and rs1110277 in the SLC23A2 gene, 49 retrospective cases, Japan) [79].

CARDIOLOGY. Anti-atherogenic properties of vitamin C have been documented, such as the beneficial effect on endothelial and collagen function through protecting arterial endothelium from formation of atherosclerotic plaques [26, 94]. Lipid peroxidation and oxidative modification of low-density lipoprotein (LDL) is a mechanism involved in the formation of atherosclerotic plaques. Vitamin C in physiological concentrations, together with vitamin E, prevents the oxidation of LDL [60]. Variations in SLC23A2 have also been associated with acute coronary

syndrome. However, in a study from 2015, no beneficial effect of vitamin C supplementation was observed on the circulatory system in subjects with SLC23A1 polymorphism [98, 109]. A 5.4-fold elevated risk of acute coronary syndrome was observed in women with the rs6139591 TT genotype who had a low intake of dietary vitamin C (936 case/1580 controls, Denmark) [26]. Women with the rs1776964 TT genotype with a high intake of vitamin C had a 3.4-fold increased risk of acute coronary syndrome compared with CC homozygotes with low intake, which, according to the authors, indicates that the effects of a genotype may not be completely compensated by high dietary intake of vitamin C [26].

OPTHALMOLOGY. Lower concentrations of vitamin C in the plasma of patients with primary glaucoma than in healthy individuals result in a weaker defense against oxidative stress. Oxidative stressis related to neuronal death. SNPs in the SLC23A2 gene have been associated with optic neuropathy and primary open-angle glaucoma (genotype rs1279386-G/G was associated with a higher risk of primary open-angle glaucoma; 150 cases/150 controls; Mediterranean population) [97, 116].

GASTROENTEROLOGY. SNPs in*SLC23A1* (rs10063949 G allele) have been associated with inflammatory bowel disease (Crohn's Disease): rs10063949AG heterozygotes had a 2.5-fold elevated risk of Crohn's disease, whereas rs10063949 GG homozygotes had a 4.7-fold elevated risk compared with wild-type homozygotes; 311 cases/142 controls [1].

DENTISTRY. It has been reported that vitamin C plasma levels are decreased in patients with periodontitis as compared to healthy controls. Searching for variants within genes SLC23A1 and SLC23A2 coding for vitamin C transporter proteins associated with aggressive and chronic periodontitis confirmed that the rare allele of rs6596473 in SLC23A1 is significantly associated with aggressive periodontitis [29].

Genetic variation in the SLC2A genes (DHA-GLUT transporter) is associated with various common complex diseases (Table 2). However, we know little about their utility as a diagnostic or a predictive biomarkers [33]. Variants in DHA-GLUT genes have been proposed to have diverse effects on the risk of nonalcoholic fatty liver disease, renal and prostate cancers, cardiovascular diseases, spina bifida, type 2 diabetes mellitus complications (albuminuria, nephropathy, retinopathy), inflammatory bowel diseases, sleep apnea or bipolar disorder [1, 10, 11, 28, 49, 63, 77, 78, 86, 96, 98, 108, 115].

VITAMIN C AND EPIGENETIC PROGRAMMING OF EMBRYO DEVELOPMENT

Epigenetics is a field of science dealing with the study of changes in the expression (readout) of genes affected by external factors [46, 87, 102]. Epigenetic modifications are a kind of molecular and cellular memory, thanks to which a change of gene expression occurs without changing the DNA sequence [52]. Examples of epigenetic modifications are 1) DNA methylation, 2) modification of histones (acetylation, methylation, ubiquitination, phosphorylation, and others), and 3) action of the so-called microRNA (non-coding single-stranded RNA molecules with a length of 19-23 nucleotides). These processes are stable in nature and can be inherited (transmitted during cell division). Epigenetic factors through regulation of gene expression affect cell differentiation and organogenesis [19]. The regulation of genes can be influenced by many factors affecting a person in everyday life, i.e. diet, sleep, physical activity, family life, professional life, and stress [19]. Elements of the body's antioxidant barrier are an important element of epigenetic regulation and a mechanism protecting against adverse effects on the reading of genetic information [39]. Vitamin C, an exogenous antioxidant delivered with food, supports an endogenous, internal antioxidant system and epigenetic reprogramming [23, 83, 87, 102]. Ascorbic acid participates in the process of programming by affecting the activity of enzymes involved in the modification of DNA and chromatin proteins. Epigenetic reprogramming occurs in mammals at early stages of embryonic development and includes demethylation and remethylation of maternal and paternal DNA [20, 46]. DNA methylation affects human development in the embryonic, prenatal, and postnatal periods as well as with aging processes [43, 76]. DNA methylation is an enzymatic process in which the monovalent methyl group -CH3 is attached at the C5 position to the cytosine incorporated in DNA in CpG, i.e. the cytosine and guanine dinucleotide in the promoter regions of genes, leading to gene silencing [43]. Lack of silencing of appropriate genes may, however, predispose to developmental disorders and diseases in adulthood (such as cardiovascular diseases, cancer, autism, or aging).

Vitamin C-dependent enzymes belong to three families: 1) the Jumonji family (histone demethylase), 2) the TET (Ten-Eleven Translocation) family responsible for demethylation of DNA, and 3) the family of AlkB proteins that are DNA/RNA demethylases [20, 64, 73]. TET proteins catalyze the oxidation of the methyl group at the 5-position of the cytosine pyrimidine ring [42]. DNA demethylation using TET proteins involves the oxidation of 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC), which can be further oxidized to 5-formylcytosine (5-fC) and 5-carboxycytosine (5-caC). Then, 5-fC and 5-caC are removed and replaced with cytosine, resulting in demethylated DNA (Figure 4) [20].

TET proteins belong to the dioxygenase family requiring Fe (II) and 2-ketoglutarate (2-KG). Ascorbic acid is an essential, specific cofactor for TET dioxygenases and it cannot be replaced by any other reducing agent [46]. The presence of ascorbic acid in the cell nucleus intensifies the activity of TET enzymes causing an increase in the level of 5-mC oxidation products which modulates the degree of DNA methylation [20]. The activity of

Table 2. Disease susceptibility resulting from genetic variation (SNPs) in Glucose Transporters (GLUTs) genes involved in the transport of dehydroascorbic acid (DHA) (adapted from Shaghaghi 2016 [98]) (NAFLD - Nonalcoholic Fatty Liver Disease, MMC – Meningomyelocele, DM2 - Type 2 Diabetes Mellitus, CVD – Cardiovascular Diseases, IBD - Inflammatory Bowel Disease)

Protein	Gene	Tissue / Cell specific expression	Transported substrate	Associated conditions	SNP (Allele)	Risk (↑↓) genotype
GLUT 1	SLC2A1 Chromosome 1p35-31.3	Brain (blood-brain barrier, glial cells), Eyes, Peripheral nerves, Placenta, Mammary glands during lactation.	Glucose, galactose, mannose, glucosamine, DHA. Responsible for glucose homeostasis in the brain. DHA transport into mitochondria.	NAFLD	rs4658 (C/G)	↑ Risk GG genotype [108]
					rs841856 (G/T)	↑ Risk TT genotype [108]
				Diabetic albuminuria	rs841847 (C/T)	↑ Risk TT genotype [49]
				Renal cell carcinoma	rs3754218 (G/T)	↑ Risk GT genotype [86]
				Spina bifida, MMC	rs2229682 (G/A)	↑ Risk A-carrier [28]
GLUT 2	SLC2A2 Chromosome 3q26.2	Kidneys, Small intestine (epithelium), Liver, Pancreas (islets), Spleen, Brain (astrocytes).	Mannose, galactose, fructose, glucose, glucosamine, DHA. Low affinity for glucose.	Impaired glucose tolerance	rs5393 (C/A)	↑ Risk AA genotype [63]
					rs5394 (C/T)	↑ Risk of type 2 diabetes T-carrier [63]
					rs5404 (G/A)	↑ Risk of type 2 diabetes A-carrier [63]
					rs5400 (A/G)	↑ Risk A-carrier [63]
				DM2	rs5400 (A/G)	↑ Risk GG genotype [96]
				Prostate cancer	rs5400 (A/G)	↑ Risk A-carrier [78]
				CVD	rs11920090 (T/A)	↑ Risk A-carrier [11]
				Bipolar Disorder	rs9875793 (A/G)	↑ Risk G-carrier [77]
					rs5398 (T/C)	↑ Risk C-carrier [77]
					rs1499821 (A/G)	↑ Risk G-carrier [77]
					rs11924032 (A/G)	↑ Risk G-carrier [77]
GLUT 3	SLC2A3 Chromosome 12p13.31	Brain, neurons, Intestinal epithelial cells, Testes, Placenta, Bone marrow.	Glucose, galactose, mannose, xylose, DHA.			
GLUT 4	SLC2A4 Chromosome 17p13.1	Adipose tissue (white/ brown), Muscles (skeletal, heart), Hippocampus and cerebellum.	Glucose, DHA, glucosamine.	Obstructive Sleep Apnea	rs5417 (C/A)	↑ Risk A-carrier [115]
GLUT 14	SLC2A14 Chromosome 12p13.31 (a duplicon of GLUT 3)	Testes, ovaries Small intestine, colon, liver Lung, heart, kidney Brain, Placenta, blood.	Glucose, DHA.	IBD (Crohn's disease, ulcerative colitis)	rs2889504 (G/T)	↑ Risk T-carrier [98]
					rs10846086 (A/G)	↑ Risk G-carrier [98]
					rs12815313 (C/T)	↑ Risk T-carrier [98]

TET proteins is of fundamental importance for normal embryonic development. Individual enzymes from the TET family are activated at various stages of fetal development [20]. Secondly, apart from epigenetic programming, the developmental process is genetic imprinting, i.e. the phenomenon of the specific behavior of the methylation pattern of the active gene from the father or mother. Genes subjected to imprinting must be protected against active demethylation carried out by TET proteins [20]. The sufficient level of ascorbic acid is one of the links in the proper course of DNA demethylation [64]. The physiological concentrations of ascorbate (11-100 μmol/L) found in human blood serum seem to be sufficient to ensure a constant level of 5-hydroxymethyl-cytosine (5-hmC) [46]. There have been many studies on the relationship between the level of 5-hmC and

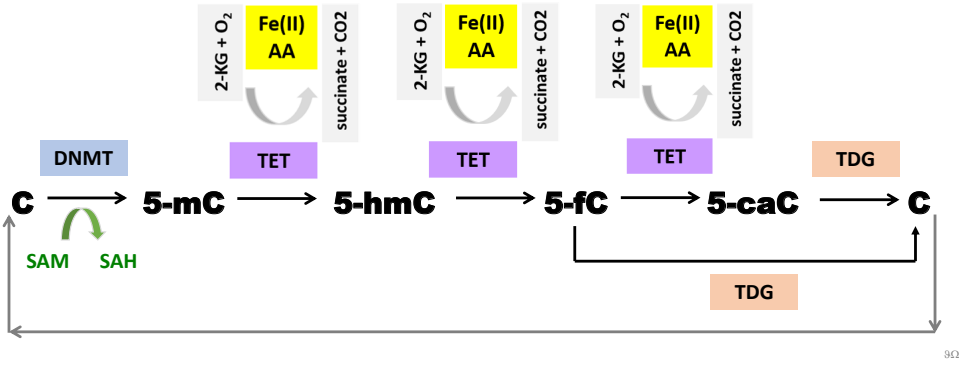

Fig. 4. DNA demethylation illustrates at which stages of the process vitamin C (AA) determines the proper functioning of TET proteins. C - cytosine; DNMT- DNA methyltransferase; SAM- S-adenosylmethionine; SAH- S-adenosylhomocysteine; 5-mC-5-methylcytosine; 5-hmC-5-hydroxymethylcytosine; 5-fC-5-formylocytosine; 5-caC-5-carboxycytosine; TET- Ten-eleven translocation enzymes; TDG- DNA glycosylase

the formation of cancer and this relationship has been confirmed in tumors of the hematopoietic system, brain, breast, colorectal, liver, lung, prostate, and pancreas [15, 20, 43, 45]. Numerous studies within the last decade have revealed that the simple addition of vitamin C to the culture media of somatic cells during reprogramming improves the efficiency and quality of induced pluripotent stem cell (iPSC) formation. As such, vitamin C has garnered great interest in the field of regenerative medicine as a stem cell therapy enhancer [64].

It is also presumed that a deficiency of vitamin C during pregnancy may disrupt genomic imprinting [37]. Parental genomic imprinting involves epigenetic modification of an allele of a gene depending on its origin, from the father or the mother, resulting in the expression of only one allele – maternal or paternal. Genetic imprinting depends on various degrees of DNA methylation within ova and sperm cells. The imprinting itself takes place during gametogenesis. The methylation pattern inherited from the parents is removed and a new pattern, depending on the gender, is applied. Transcription factors cannot attach to the methylated nucleotide, which results in gene silencing. This imprinted expression of a small number of genes is crucial for normal development, as these genes often directly regulate fetal growth and brain function with important consequences on behavior and neuronal function [89]. Loss of this imprinting is associated with diseases such as Prader-Willi syndrome, Angelman's syndrome or Silver-Russell Syndrome.

PREGNANCY – A TIME OF INCREASED VITAMIN C REQUIREMENT

Vitamin C requirements are increased during pregnancy as the vitamin is actively transported across the placenta in response to the needs of the growing fetus. Additionally, decreased plasma vitamin C levels result from physiological hemodilution and inadequate intake [51, 92]. Moreover, increased oxidative stress during pregnancy increases the need for antioxidants and vitamin C is one of the major players here. Vitamin C, in addition to copper and magnesium, participates in biochemical processes responsible for the strength and elasticity of fetal membranes. Premature rupture of fetal membranes results from collagen cracks in the extracellular matrix due to amniotic and choroidal disease and programmed death of the membranes [88]. Research on the effects of vitamin C on the course of pregnancy initiated over fifty years ago is still being carried out today and positive pregnancy and infant outcomes resulting from dietary vitamin C intake or supplementation have been described [21, 35, 74, 111]. Siega-Riz et al. showed that inadequate coverage in the diet of the daily requirement for vitamin C during pregnancy and reduced ascorbic acid in the serum, white blood cells, and umbilical cord blood are associated with a risk of premature rupture of fetal membranes and preterm delivery (<37 week of gestation) [101].

The safe dosage of vitamin C as recommended by the American Pregnancy Association is 80 to 85 mg daily, while the National Institute of Health's Medline Plus suggests that pregnant women consume around 120 milligrams daily, mainly by eating plenty of fresh fruits and vegetables rather than by supplements [92]. An8-oz (240 ml] cup of orange juice contains around 82 mg of vitamin C and can fulfil most of the daily requirement. A dietary vitamin C intake above 200 mg/day during mid-pregnancy may reduce the risk of gestational diabetes mellitus [71]. Maternal fruit and vegetable consumption or vitamin C supplementation at mid-pregnancy was associated with increased fetal growth and infant growth up to 6 months of age in a large Korean cohort study involving 1,138 pregnant women [51]. Daily supplementation of 500 mg of vitamin C (started at <22 weeks of gestation) administered to women who would not quit smoking during pregnancy improved newborn pulmonary function and decreased the incidence of wheezing through the 1 year of life, prevented offspring DNA methylation, and protected infant lung function [100].

The efficacy and safety of vitamin C supplementation in pregnancy was previously (2015) analyzed in a Cochrane review encompassing 29 trials [92]. Vitamin C supplementation in pregnancy (alone or in combination with other supplements, mainly vitamin E) was associated with a 36% reduced risk of placental abruption (RR 0.64, 95%CI 0.44 to 0.92; eight studies; 15,755 participants) and a small increase in gestational age at birth (MD 0.31, 95% CI 0.01 to 0.61; nine studies; 14,062 participants) [92]. Vitamin C supplementation alone was associated with reduced risk of preterm PROM (average RR 0.66, 95% CI 0.48 to 0.91; five studies; 1282 participants) and reduced risk of term PROM (average RR 0.55, 95% CI 0.32 to 0.94; one study; 170 participants). However, further research is required to confirm these findings due to the heterogeneity of the studies (of 29 included trials 11 were judged as low risk of bias); with varying spectrums of health conditions of the included women (healthy vs. at high risk pre-eclampsia, essential hypertension, nephropathy, type 1 diabetes, BMI ≥30 kg/m^2); various timings of supplementation commencement, from 4 weeks (1 study) to ≥35 weeks (1 study), in most of the studies entry was at 20 weeks' gestation; various intervention combinations (vitamin C alone in 12 studies, vitamin C in addition to vitamin E in 15 studies, or with other medications or supplements such as allopurinol, aspirin, fish oil, iron, folic acid, vitamin B, calcium, prenatal vitamins); and varied daily vitamin C supplementation (in 15 studies the most common daily dosage of vitamin C was 1000 mg with other studies giving dosages of 100 mg, 250 mg, 400 mg, 2000 mg; in one study vitamin C was administrated vaginally). Dietary intake of vitamin C at baseline was either not assessed or not reported in the majority of trials included in this systematic review. Despite incomplete data on supplementation of ascorbic acid, maternal nutrition during pregnancy is a major determinant of current and future mother and child health outcomes.

RESTRICTIONS ON THE USE OF VITAMIN C

While paying attention to the many positive aspects of vitamin C's physiological effects, it is necessary to keep in mind the potential adverse effects after consumption of doses exceeding recommended values (the RDA). Increased dietary intake of antioxidants is generally regarded as safe and without undesirable side-effects in healthy persons [30]. Special attention must be paid to individuals on high-dose ascorbic acid regimes and with coexisting medical conditions. Organs particularly susceptible to adverse effects of high doses (250 mg-15 g per day) of vitamins are the gastrointestinal tract, kidneys, and hematopoietic system [75]. Gastrointestinal symptoms of excessive vitamin C supply commonly described include nausea, vomiting, heartburn, bloating, and osmotic diarrhea with accompanying headaches, redness of the face, sleep disturbances, fatigue, and deterioration of mental functions [6]. Vitamin C as a metabolic oxalate precursor promotes oxalate precipitation in urine (hyperoxaluria) predisposing to oxalate nephropathy and should be used with caution in patients with kidney stones [4, 80]. It should be noted that there is no dose-response relationship between administered vitamin C and excreted oxalate and that other factors are involved, such as urate excretion or alkalinity of urine [30]. With administration of high doses of vitamin C, the possibility of forming oxalate crystals and their accumulation in various organs increases, not only in kidneys, but also in the muscles (presenting as myalgia), the myocardium, in the lungs, or in the heart and nervous systems, notably in people with co-existing kidney or digestive tract diseases, the immunocompromized, or (and especially) those genetically predisposed to hyperoxaluria [62, 80, 91, 93, 104, 114]. Vitamin C in a daily dose of 4-8 g may affect uric acid secretion in the urine, provoking attacks of gout in predisposed individuals [80]. Vitamin C increases the absorption of iron which may lead to an overloading of the body with iron. As such, it is contraindicated in people with elevated serum iron levels possibly being unsafe for patients with hemochromatosis, thalassemia, and sideroblastic anemia. Vitamin C over-supplementation increases the risk of hemolysis in patients deficient of the glucose-6-phosphate dehydrogenase. While ascorbic acid decreases the risk of developing dental caries, chronic use of vitamin C in the form of chewable tablets may reduce the pH of saliva by reducing the amount of calcium from enamel sources, leading to damage of enamel and increased severity of caries.

Vitamin C if taken at the same time as other medicines may increase the effects and toxicity of these drugs (such as oral anticoagulants and sulfonamides). Research on the interaction of ascorbic acid with vitamin B12 had led to vitamin C being suspected of reducing vitamin B12 bioavailability andplasma levels. Vitamin C supplements were recommended to be taken two or more hours after vitamin B12 supplements [30, 92]. However, this effect was later found to be a result of an analytical error [30].

Ascorbic acid may also interfere with blood and/or urine results causing false negative laboratory tests (assessment of glucose, creatinine, uric acid, LDH, AST, hemoglobin, bilirubin, protein, nitrates, leukocyte esterase, carbamazepine, acetaminophen, theophylline) [107]. A daily dose of 250 mg may result in a false negative stool test for occult blood, which is why vitamin C supplementation should be discontinued at least 2 weeks before this test.

CONCLUSION

Recent years have seen an increase in the number of studies on genetic and epigenetic aspects of vitamin C as a regulator of the epigenome. This is especially true regarding the course of pregnancy, prenatal and postnatal programming as well as late sequelae resulting in neoplastic, neurodegenerative, and autoimmune diseases. The particular, epigenetic role of vitamin C starts at the beginning of life, especially in the first weeks after conception with an influence through genomic imprint-

ing on embryonal human development [37, 100, 110]. Its role includes regulation of DNA methylation, one of the basic mechanisms for regulating gene expression [38, 46]. Vitamin C, a micronutrient and an epigenetic regulator, is an example of the interplay between the environment and the genome, the area of research encompassed by nutrigenomics. Vitamin C is also of great interest in the field of regenerative medicine as a stem cell therapy enhancer and modulator of epigenetic dysregulation in cancer patients.

The pleiotropic effects of vitamin C are essential for many physiological functions in the body as a cofactor necessary for the proper course of many biochemical transformations. Variants (SNPs) of genes encoding vitamin C transport proteins are associated with the uptake of vitamin C from food, reabsorption in the kidneys, and further distribution in tissues. Vitamin C, as an essential micronutrient, is one of the elements of a defensive antioxidant system that protects against damage to cell membranes and DNA. Both accumulation of free radicals and lipid peroxidation increase with age and the elderly as well as those exposed to oxidative stress are in need of vitamin C's protective support. Neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, or ischemic stroke are characterized by a significant overproduction of free radicals. The most efficient in protecting against free-radical damage to DNA are fresh vegetables and fruits containing ascorbic acid, as advised by WHO and FAO (FAO/WHO 2004). Consuming 5 servings of fresh and cold vegetables and fruits daily allows for a constant supply of vitamin C and prevents its deficiency.

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