Chapter

Supplements and Down Syndrome

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Abstract

Down syndrome (DS) is one of the most common genetic disorders associated with a number of difficulties that are visible through the motor and cognitive development. Some theories claim that intake of supplements in very high doses could upgrade the physical and intellectual status of individuals with DS. Numerous papers have been published to support these theories, but at the same time, a great number of papers have warned of the risks of uncontrolled, excessive use of dietary supplements and asked for the proof of such claims by independent scientific studies. In this chapter, we will provide a review of the most commonly used supplements and major findings on this matter. Open access to information about the positive and negative sides of such supplementation is primarily important for guardians of people with DS in order to make the decision whether to use such preparations. It could also be an incentive for scientists to focus on the development of beneficial and safe therapies.

Keywords: Down syndrome, trisomy 21, oxidative stress, supplements, genes

1. Introduction

The aim of this chapter is to provide the reader with scientifically based information about the possibilities and dangers of using nutritional supplements for individuals with Down syndrome (DS). DS or trisomy 21, first described by Dr. John Langdon Down in 1866, is one of the most common genetic disorders that impact fetal development. It is a chromosomal disorder where an individual has an additional copy of chromosome 21, which may be full or partial [1]. The prevalence of children with DS worldwide is between 1:319 and 1:1000, and depends on the age of the mother (1/2000 in teenage girls to 1/40 in 42-year-old women) sociocultural, religious variables, and the possibility of terminating a pregnancy [2–4]. Every child with DS has unique phenotypic characteristics on which their overall physical and cognitive development depends, so the medical conditions associated with DS are not the same for every child (**Figure 1**). Considering the high cure rate of various comorbidities from which a DS child can suffer before and after birth, the mortality rate fell from 14.2% to 2.3% [5]. The life expectancy of people with DS has increased significantly over the last century, up to 60 years [6]. The use of nutritional supplements for children with DS is a topic that is extremely important for parents and caregivers as they want to improve their child's cognitive functions and health. However, the danger to the child can arise when the use of dietary supplements is uncontrolled, in large doses, and without a prior nutritional status of the organism. The program of early intervention with dietary supplements has been increasingly mentioned in connection with DS,

Figure 1.
A three-year-old child with Down syndrome. (source: author).

however, research on the benefits of their use is still very unsupported by concrete evidence that would give doctors guidance for their recommendation.

2. Down syndrome

Since the discovery that DS is a result of trisomy 21, the main interest of the studies has been the identification of human chromosome 21 genes (Hsa21), and the impact of their overexpression on the DS phenotype [7]. To explain the similarities and differences in the phenotypic characteristics associated with DS, a gene dose imbalance theory has been hypothesized stating that patients with DS have an increased dose or number of gene copies on Hsa21, which may lead to increased gene expression. This includes the possibility that specific genes or subsets of genes can control specific phenotypes of DS, but also that a nonspecific dose of a number of trisomic genes leads to a genetic imbalance that has a major impact on the expression and regulation of many other genes throughout the genome. Phenotypic analyzes found that only one or a few small chromosomal regions, termed "critical regions of Down syndrome," (DSCR) a region of 3.8–6.5 Mb at 21q21.22, with approximately 30 genes are responsible for most DS phenotypes [8, 9]. There are numerous physical features and congenital conditions specific to DS, resulting from overexpression of genes caused by the extra chromosome presented in **Table 1**. Every child is unique and features and conditions are not equally expressed and represented.

Physical features	
Head	Small, shortened skull that is flattened on the back, sloping forehead, missing or underdeveloped sinuses.
Eyes	Upward slanted and wide-set eyes, brushfield spots, and epicanthal folds.
Ears	Ears set lower on the head and smaller ears with extra folds.
Nose	Smaller nose and flattened nasal bridge.
Mouth	Smaller mouth, large tongue that tends to stick out more often, undersized teeth, crooked teeth, and irregularly shaped teeth.
Hands	Short fingers, broad hands, only one crease across the palm, and curved fifth finger.
Feet	Larger gap between the first and the second toe.
Limbs	Short and stocky arms and legs with hyperflexible joints.
Body	Short stature, shorter and wider neck, protruding stomach.
Congenital condition	
Heart	Septal defects (atrial septal defect, ventricular septal defect, and atrioventricular septal defect), patent ductus arteriosus, and tetralogy of Fallot.
Vision	Glaucoma, refractive errors, cataracts, amblyopia, and blepharitis.
Hearing	Hearing loss (conductive and sensorineural), glue ear, and otitis media.
Musculoskeletal	Hypotonia, ligamentous laxity, atlantoaxial instability, hip abnormalities, kneecap instability, and flat feet.
Digestive	Hirschsprung disease, tracheoesophageal fistula, duodenal atresia, esophageal atresia, imperforate anus, and gastroesophageal reflux disorder.
Immune	Hypothyroidism, respiratory infections, and celiac disease.

Table 1.
Possible physical features and congenital conditions associated with Down syndrome [9].

Promoting the health of people with DS is extremely important because it creates a prerequisite for improving their quality of life. Dietary composition, macronutrient and micronutrient intake, eating habits, and lifestyle can be fundamental for maintaining good health. Proper nutrition can have a major impact on preventing or delaying the onset of certain diseases in people with DS. However, very often nutrients from food are not enough to fulfill the daily needs for basic nutrients due to difficulties with swallowing and chewing, excessive sensory sensitivity, and numerous health problems, such as celiac disease. Cardiopathy in infants can impair food tolerance and adverse conditions may increase the frequency of aspiration [10].

In order to compensate for the lack of key nutrients necessary for the proper functioning of the body and fill the gap between diet and health in children with DS, dietary supplements can be used, but their usage should be controlled and in accordance with the identified deficiencies in the body.

3. History of nutritional supplementation for DS

Based on the assumption that an extra chromosome causes a metabolic imbalance that can be affected by various dietary supplements, Dr. Henry Turkel developed

the first formulation composed of 48 different substances called “U-series” in the 1940s. The Food and Drug Administration (FDA) rejected his request for a new drug because it could not serve as a cure. A modified supplement formula was developed by Dr. Jack Warner during the 1980s as high-performance capsules (HAP Caps), which contained high doses of dietary antioxidants, such as vitamins A, E, and C, digestive enzymes, minerals zinc (Zn), copper (Cu), manganese (Mn), and selenium (Se), in order to correct metabolic disorders. HAP caps were formulated in the FDA laboratory and had approval from 1986 until his death in 2004 [11, 12]. During this period, Dixie Lawrence Tafoya, combining elements of both treatments with the addition of new ingredients, developed a combination of targeted nutritional intervention (TNI) supplements that included amino acids and smart drugs (Piracetam) in addition to various micronutrients. These supplements were promoted under the name Nutrivene. In Canada, under the leadership of Kent Macleod, Nutrichem Laboratories has launched a supplement called "MSB Plus" in accordance with the standards of good manufacturing practice at the licensed Health Canada Site. Despite the fact that various supplements have been applied to children with DS since the 1950s, repeated studies have shown that there are no nutritional deficiencies that would apply to all children with DS. Furthermore, there is no objective study that has confirmed the need for any of these supplements, with the possible exception of the minerals Zn and Se [12, 13].

Sacks & Buckley [12] pointed out the lack of well-designed scientific studies and warned of the danger of overdose in the case of supplement introduction in addition to a balanced diet. Many studies that support supplementation involved a small number of subjects, a wide range of age participants, short duration, and very few randomized controlled and blind studies [14, 15].

The popularity of supplements was confirmed by a survey among 1,200 respondents in the US, Brazil, and the EU that found that almost half of pediatric patients with DS have used or are currently using dietary supplements. 20% of surveyed parents who gave their child supplements haven’t informed the pediatrician about it. Above all, supplements given to children with DS often exceeded the recommended daily doses [16]. Nevertheless, dietary supplements for DS still receive a lot of attention from parents, which leads to efforts of scientists to define the possible benefits of dietary supplements for people with DS-based on scientifically based knowledge.

4. DS issues targeted by nutritional supplementation

4.1 Oxidative stress

The theory of oxidative stress involves the occurrence of oxygen radicals, called reactive oxygen species (ROS) during oxidative metabolism. ROS include superoxides ($O_2 \bullet^-$) and hydroxyl (OH •) free radicals and other molecules, such as hydrogen peroxide (H_2O_2) and peroxynitrite which have the ability to become very harmful to cells. To defend against ROS, cells developed various mechanisms to eliminate them: antioxidant enzymes (superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT)) along with antioxidants, such as vitamins C, E, or glutathione. If an imbalance between oxidants and antioxidants happens in cells, oxidative stress occurs [17, 18]. Numerous studies point to oxidative stress as a possible explanation for a number of DS-related problems, such as intellectual disability, accelerated aging, and cognitive and neuronal dysfunction [14, 19–21].

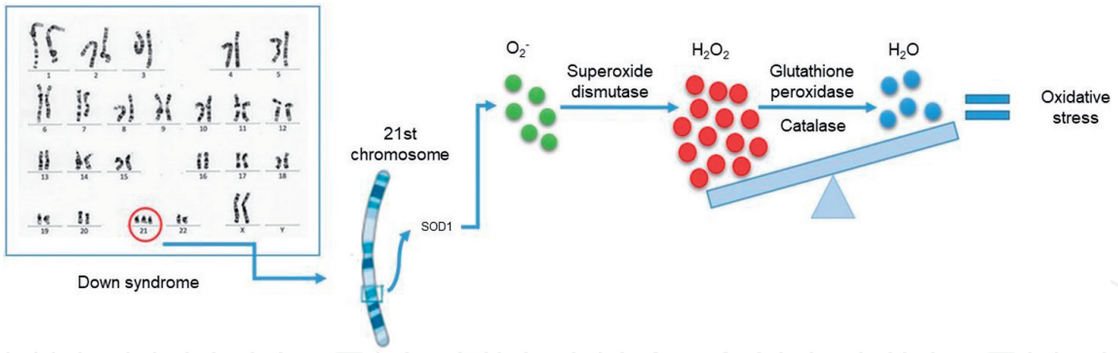

Figure 2.
Oxidative stress in Down syndrome.

The 21st chromosome contains SOD1 gene, which encodes the enzyme Cu-Zn superoxide dismutase (Cu-Zn SOD), responsible for the conversion of O_2^- to H_2O_2 in the cytosol. Increased SOD1 activity results in the creation of elevated levels of H_2O_2 that should be effectively removed by other enzymes, such as CAT, GPx, and thioredoxin peroxidase. Excess of chromosomes leads to overexpression of the SOD1 gene, and to elevated H_2O_2 levels that cannot be completely eliminated by CAT and GPx, so overproduction of ROS occurs (**Figure 2**) [22–25]. SOD1 was found to be 50% higher than normal in various cells and tissues of people with DS, so the SOD1/GPx activity ratio was consequently altered [19, 22, 26–29].

Strydom et al. [30] in his study on 32 adults with DS could not confirm the hypothesis that an increased SOD1/GPx ratio leads to low cognitive results. Surprisingly, they found that a low SOD1/GPx ratio leads to bad memory ability. They also pointed out that other possible factors could also affect SOD1 and GPx activity, such as regular exercise, Se, and homocysteine levels.

4.2 Cognitive development

Research has shown that the maturation of certain areas of the brain during childhood is associated with the development of specific cognitive functions, such as language, reading, and memory [31, 32]. Rapid brain growth occurs during the first 2 years of life (at age 2, the brain reaches 80% of an adult's weight), so this period of life may be particularly sensitive to nutritional deficiencies [33].

Nutrition, as the link between nutrients and health, should provide the building blocks needed to build and maintain the structure and function of the central nervous system. The intellectual disorder occurs when a child fails to fully develop the intellectual ability to think, reason, learn and understand. Children with intellectual disabilities also have problems in learning adaptive behavior, which encompasses the social and practical skills needed for everyday life. Intellectual impairment varies among children with Down syndrome. It ranges from a severe intellectual impairment that makes people completely dependent on caregivers, to mild effects that allow people to think and learn at levels that allow them to continue their higher education, keep their jobs, and live independently.

It is thought that nutrition may play a key role in brain development, and, thus intellectual functioning. The brain, similar to the rest of the body, needs proteins, fats, carbohydrates, vitamins, and minerals to grow and function, which are ingested through food or supplementation if food intake is difficult. As the brain develops faster than the rest of the body, it is obvious to consider that a lack of nutrition at

a critical stage of development can lead to permanent changes in the structure and functioning of the brain. In addition, the brain is the most metabolically active organ in the body, but it has very limited energy reserves, so it relies on a diet for a continuous supply of glucose. Similarly, minute-by-minute brain function requires an adequate supply of micronutrients that act as coenzymes or form structural parts of enzymes required for optimal metabolic activity [34, 35].

4.3 Neurodegenerative diseases

Since individuals with DS are prone to elevated levels of oxidative stress at an early age and consequent accumulation of ROS, which are cytotoxic byproducts of normal mitochondrial metabolism, there is an insufficient defense of endogenous antioxidants. In this case, oxidative molecules can disrupt cellular functions by affecting synaptic plasticity, ultimately leading to neuronal injury and apoptosis. Individuals with DS over the age of 35 have a higher frequency of short-term memory impairment and an increase in the rate of dementia, aphasia, and agnosia, while executive function impairments are evident as early as adolescence. One of the most important genes associated with DS is amyloid precursor protein (APP), a gene encoded on chromosome 21. Increased APP production may contribute in part to oxidative stress associated with neurodegenerative diseases and inflammation. Accumulation of amyloid-beta monomers can directly disrupt mitochondrial function resulting in reduced energy and accumulation of amyloid plaques leading to activation of inflammatory cascades [36, 37].

Alzheimer disease (AD) is a form of dementia that can most commonly develop in people with DS, as in the general population. Unfortunately, effective drugs have not yet been developed to be available to treat dementia in DS. Prevention is crucial to alleviate the symptoms of neurodegenerative diseases, but also to delay them. Detection of biomarkers and the development of sensitive cognitive screening tools will be essential for earlier diagnosis and better therapeutic management [38]. There are numerous studies on how to reduce or slow down the course of neurodegenerative diseases, such as AD, in people with DS. The causes of AD in people with DS is associated with overexpression of genes and lack of nutrients due to poor diet can be influenced by regulation of endogenous antioxidants, intake of vitamins, minerals, polyunsaturated fatty acids, and polyphenols [39–42].

5. Commonly used nutritional supplements for individuals with Down syndrome

5.1 Vitamins

As explained in the previous chapter, increased oxidative stress in individuals with DS is present from early life, leading to lipid peroxidation and DNA damage [43]. For that reason, antioxidant vitamins have been the focus of many research (**Table 2**). Vitamin E, especially its form known as α-tocopherol, is a strong antioxidant, important for the prevention of oxidation of unsaturated fatty acids in cell membranes [49, 50]. Some studies involved trisomy 16 mouse models in order to get a basis before clinical trials on DS humans because these mice have increased oxidative stress and cerebral pathology similar to DS [51–54].

Experimental group	Vitamin	Duration of trial	Result	Ref.
Randomized, placebo-controlled study, 20536 adults aged 40–80	600 mg/day vitE 250 mg/day vitamin C 20 mg/day of carotene	5 year treatment period	No improvement in cognitive abilities, no significant differences in all-cause, and vascular and non-vascular mortality.	[44]
93 children with DS aged 7–15 years, 26 non-DS siblings in the same age range as a control group	400 IU vitamin E	4 months	No change in TBARS levels and reduced 8-OHdG levels.	[21]
Randomized double-blind study, 53 individuals with DS	900 IU α-tocoferol, 200 mg ascorbic acid, 600 mg α-lipoic acid	2 years	No improvement or stabilisation of dementia.	[45]
5092 elderly people (90% aged 65 years and older)	Various combinations of vitamin E, C, and multivitamins	3 years	Combination of vitamins gave positive results in prevalence of Alzheimer's disease.	[46]
156 infants aged under 7 months with trisomy 21	100 mg vitamin E, 0 mg vitamin C, 0,9 mg vitamin A, 10 μg Se, 5 mg Zn, and 0,1 mg folinic acid	18 months	No effect on SOD, GPx activity and SOD/GPx ratio, no effect on Griffiths developmental quotient, and an adapted MacArthur communicative development.	[27]
21 children with DS, 18 healthy children	400 mg vitamin E, 500 mg vitamin C	6 months	Decrease of erythrocytic SOD and CAT, and decrease of GPx activity in DS children.	[47]
160 adults with trisomy 21 and 160 healthy, unrelated subjects aged 26 ± 4 years	5 mg/day folic acid, 5 mg/day vitamin B6, 100 μg/day B12 alone or in combination	–	No significant differences in fasting blood tHcy concentrations between healthy controls and adult trisomy 21 patients that justify B vitamin supplementation.	[48]

Table 2.
Examples of vitamin supplementation research for DS individuals.

Lockrow et al. [43] suggested that transgenic mice could be used in order to get insight into the molecular pathways of the disease and to test the efficiency of drugs. They also warned that mice do not manifest all the features as humans do. Still, they proved a correlation between high oxidative stress in transgenic mice and low working memory. The introduction of vitamin E to the diet of mice gave positive results on oxidative stress and neuronal markers. They also suggested that this could be a good starting point for the treatment of neurodegenerative diseases, such as DS and AD, in humans. Lott [55] pointed out that clinical studies on humans still did not provide satisfactory results, although animal studies in oxidative stress are promising.

As presented in **Table 2**, studies on humans had very different experimental groups in the number of participants, age, and dosage of supplements. The

conclusions they obtained were also very different. Lockrow et al. [43] and Lott [55] suggested that vitamin E supplementation could exhibit better results if implemented at younger age as preventive therapy for dementia, but it requires additional clinical trials. Tanabe et al. [56] could not find a correlation between elevated Cu-Zn SOD activity and cellular vitamin E status in DS.

It can be seen that a combination of vitamins E and C have been commonly used. Vitamin C helps to maintain a stable concentration of vitamin E in plasma by protecting it from damaging oxidation and keeping it in the active state [49, 57, 58]. The link between cognitive decline in AD and vitamin C intake has been studied by Harrison [18]. He included many studies involving vitamin C or a combination of vitamin C and E in his review article. Contradictory results regarding the usefulness of high doses of vitamin C for the cognitive decline have been provided, but a high connection between the low consummation rate of fruits and vegetables and bad cognitive function has been undoubtfully proved. So, prevention of deficiency by quality nutrition should be the first line of defense against cognitive decline instead of supplementation.

It is very important to remember that high doses of supplements can lead to organ damage, harmful interactions, and toxicity [59]. Besides, reactive oxygen species are necessary for obtaining normal cell functioning, so implementation of high doses of antioxidant supplementation would remove too much ROS disrupting cell signaling pathways [60, 61]. The dietary institute for medicine recommends 22 IU RDA for vitamin E and 75 to 90 mg for vitamin C, which is much lower than the doses usually present in supplements (up to 1000 IU of vitamin E and up to 1000 mg of vitamin C) or which have been used in previously mentioned studies [62].

The deficiency of B12 vitamin is mainly associated with a vegetarian and vegan diet, since it mainly originates from animal products. B12 deficiency in infants can lead to various clinical symptoms, such as hypotonic muscles, involuntary muscle movements, apathy, cerebral atrophy, and demyelination of nerve cells [63, 64]. It has an important role in brain function and development through methylation reactions in the central nervous system. Vitamin B12 is also a cofactor in numerous catalytic reactions in the human body, which are required for neurotransmitter synthesis and functioning. Vitamin B12 deficiency can also result in neuropathy through degeneration of nerve fibers and irreversible brain damage [65]. Folates are also B group, water-soluble vitamins, which serve as coenzymes in a variety of reactions. Numerous enzymes involved in folate transport and metabolism are encoded by genes located on chromosome 21 and represent a potential mechanistic basis for folate dysregulation in children with DS. Potential genetic causes of metabolic folate dysregulation in children with DS, non-genetic factors, such as diet, gender, and age, must be considered because they must fully satisfy their folate needs through their diet since they lack the enzymatic machinery necessary to synthesize their own. There are two possible mechanisms for the influence of folate and vitamin B12 deficiency on the brain: by disrupting myelination or influencing the inflammatory process [66, 67].

Individuals with DS have higher plasma homocysteine concentration than healthy people. There are several possible reasons for changes in its metabolism. The deficiency of vitamin B6, B12, and folic acid is one of the theories explaining the accumulation of homocysteine because those vitamins are important cofactors for its metabolism. High plasma concentration is a result of a high cytotoxic intracellular homocysteine. It is assumed that this is a repercussion of gene overexpression on chromosome 21 [68, 69]. Studies [14, 70–73] proved that intake of high doses of B group vitamins reduced homocysteine levels and reduced the rate of brain atrophy in

individuals with mild cognitive deterioration. On the other hand, Fillon-Emery et al. [48] presented results, which showed that the plasma homocysteine concentration of individuals with DS who did not take supplemental vitamins was not significantly different from that of controls. [74, 75] also warned that research on vitamin B supplementation gives contradictory results without scientific evidence for cognitive improvement.

5.2 ω-3 fatty acids

There are numerous roles of dietary lipids essential for the proper function of cells. They are building material for cellular membranes and bioactive molecules, serve as a source of energy, take part in cell signaling pathways and participate in the regulation of gene expression. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are essential polyunsaturated fatty acids with an omega-3 desaturation that cannot be synthesized in the human body [76].

In total, 60% of the dry weight of the human brain are lipids, of which 20% are DHA and arachidonic acid (AA; an omega-6 fatty acid) the two core fatty acids found in gray matter. For that reason, there is a high interest in the influence of unsaturated fatty acids, especially essential ones, for cognitive brain development [77].

Adequate intake of omega-3-fatty acids is crucial for the normal functioning of brain tissue. As already mentioned, as parts of cell membranes, they influence membrane fluidity and modulate ion channels. They are also important in inflammation and immune reactions, as well as for signal processing and neural transmission [77–79].

5.3 Minerals

Due to the fact that SOD and GPx, important enzymes involved in oxidative homeostasis of the cells, contain Se and Zn, these minerals are considered as crucial antioxidant vitamins [80, 81]. Some of the studies about the influence of mentioned minerals on DS individuals are presented in **Table 3**. Besides its role in antioxidative enzymes and metabolism, Se influences serum concentrations of IgG2 and IgG4 in children with DS. DS children are very sensitive to respiratory bacterial infections, and it has been proved that Se concentration decreases after severe bacterial infection. In that light, intake of Se could be beneficial for children with DS as a part of the immune response to bacterial antigens [89]. Se is also important for the production of thyroid hormones. The thyroid gland tissue contains a high concentration of Se [90]. In the case of Se deficiency, H_2O_2 gets accumulated and oxidative stress increases that lead to cell apoptosis [91]. Adequate Se intake is necessary for proper intracellular GPx functioning and protection of thyrocytes from peroxides [26]. Hypothyroidism is common in people with DS, so Se supplementation could be useful in that case [92]. The same as already mentioned for vitamins, adequate intake of Se by proper diet should be considered first. The bioavailability of Se originating from proteinaceous food (meat, fish, shellfish, eggs, and cereals) varies from 20% to 80% (the best is from cereals and yeast). It is mainly in the form of selenomethionine. In supplements, the inorganic form of Se, sodium selenite, is mainly used and has excellent bioavailability [91, 93, 94].

Zinc deficiency slows growth because it is involved in the activity of more than 200 enzymes, especially those associated with the synthesis of RNA and DNA. It is important for the function of numerous enzymes and transcription factors [95].

Experimental and clinical studies have found that zinc metabolism is altered in individuals with Down syndrome (**Table 3**). Lima et al. [85], reported that adequate

Experimental group	Mineral	Duration of trial	Result	Ref.
29 trisomy 21 patients 9 to 36 years and 32 age-matched controls	Measurement of Zn, Cu, and Se level	–	Mean plasma Zn and Cu level of DS subjects were not different from that of the control group. Mean plasma Se was significantly decreased in DS subjects, and activity of GPx was significantly increased in the DS group.	[82]
Group aged 1 to 54 years	Supplementation of Na–selenite in a dose of 0.015–0.025 mg/kg/day	0.3–1.5 years	GPx activity increased by 25%, and the SOD1/GPx ratio decreased by 23.9% in the Se group.	[83]
18 DS children aged from 8 months to 3 years with trisomy 21, translocations, and mosaicism, and control group of 15 children	Measurement of the activities of SOD and GPx, and the levels of their cofactors Cu, Zn, and Se	–	Insufficient concentrations of Se in individuals with DS, Cu levels significantly higher in DS groups, and plasma Zn concentrations were normal. Whole-blood Se levels were decreased significantly in all patients compared to controls, with no correlation between whole Se levels and GPx activity. SOD and GPx activity do not show a correlation with clinical manifestations of DS.	[84]
35 children with DS and 33 controls both aged 4–11 years	Zn in plasma, urine, and erythrocyte	–	Decreased Zn levels in the plasma and urine of DS subjects in comparison to the control group, and erythrocyte Zn levels were adequate.	[85]
30 children with Down syndrome	Measurement of Zn level	5 years	Up to 5 years of age, plasma Zn levels are adequate but tend to decrease after this age.	[86]
38 DS children 2–15 years old, 20 healthy children aged 2–14 years	Measurement of serum concentration of Zn and Ig before and after 20 mg/kg/day of zinc sulfate for two months.	2 years	Low plasma Zn levels in DS patients, but no correlation was found between the Zn deficiency and the recurrence or intensity of infections. Low serum Zn levels in some DS children increased after supplementation. No difference between DS children and control in the percentage of B lymphocytes, and serum IgG, IgA, and IgM levels.	[87]
19 children with DS 2–6 years old and 11 age-matched controls	Measurement of hair zinc levels	–	Hair zinc levels are significantly lower in those with Down syndrome.	[88]

Table 3.
Examples of research on mineral status in DS individuals.

zinc intake was observed in 40% of children with DS and in 67% of the control group and zinc concentrations were significantly lower in plasma and urine and higher in erythrocytes of children with DS. There are several possible reasons for that: low plasma Zn concentration could be a result of a redistribution of a mineral in an organism, and not an inhibition of its absorption. A high level of erythrocytes Zn may be a consequence of increased Cu-Zn SOD activity. If DS children are iron deficient (which occurs quite often), Zn binds to the protoporphyrin instead of the iron [85]. Many symptoms of children and adults with DS are a consequence of excessive synthesis of multiple gene products, including an increase in the intracellular activity of Cu-Zn SOD due to overexpression of genes present on chromosome 21. Zinc stabilizes the 3D structure of SOD, and, thus reduces the imbalance [85]. It also participates in the formation of thyroid hormones, leucocytes, and antibodies [49, 96, 97].

5.4 Polyphenols

Mitochondria are the primary site for the creation of free radicals due to the production of adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS), so elevated oxidative stress in individuals with DS primarily affects these organelles. DS individuals have decreased efficiency in producing ATP and reduced respiratory capacity. Mitochondria dysfunction primarily influence brain functioning because of its high susceptibility to energy deficit [98].

Epigallocatechin gallate (EGCG) originating from green tea has been studied in mouse and cell models, and it has been found that it is effective as a ROS scavenging agent, mitochondrial apoptosis protector, mitochondrial bioenergetics activator, and respiratory chain promotor [98, 99]. On the other hand, *in vivo* tests found that EGCG bioavailability is low, due to poor absorption and metabolic modification. It is still unknown whether metabolites reach the brain and influence cell metabolism [99]. Torre and Dierssen [75] warned that many clinical trials in DS patients have limitations, such as poor design, a reduced number of participants, a lack of methods for the neuropsychological evaluation of patients, and the dependence on the IQ of individuals.

It is considered that concentrations of polyphenols normally present in foods are too low to exhibit a beneficial effect on metabolic pathways, so supplementation should be implemented in the daily routine of individuals with DS [100]. This opens an important question about the dosage. Namely, EGCG in high doses acts as a prooxidant with harmful effects on skeletal DS phenotypes, liver, kidney, thymus, spleen, and pancreas [101, 102]. 10 mg/kg/day of EGCG has been found as safe, and effective on mitochondrial and behavioral dysfunction by a case study on a 10-year-old DS child. Although studies on mouse models targeted doses of 10/mg/kg/day–50 mg/kg/day as harmful without positive effect [100]. Long et al. [102] in his survey found that commercially available preparations ranged from 351 mg/day to 2000 mg/day. Some respondents included in this survey reported improvement in speech, memory, learning, and energy, while the others quit supplementation due to the lack of improvements.

Research provided by Xicota et al. [103] tried to determine the influence of EGCG supplementation (9 mg/kg) on body weight. It is considered that EGCG decreases the absorption of lipids and glucose. The survey followed the DS group during 12 months of supplementation and additional 6 months after quitting the treatment. Male subjects exhibited less body weight gain, unlike female subjects, but the authors did not provide an explanation for such results and further research should be done in order to confirm these findings.

Resveratrol originating from different berries, grapes, red wine, and peanuts is another polyphenol used as a therapy for the improvement of mitochondrial functions and diminishing some of the DS clinical features [100]. The same as already mentioned for EGCG, bioavailability is low and its original form quickly changes into metabolites [104]. Studies on the experimental rats determined doses of 700 mg/kg/day as safe [104]. Considering the fact that it is not the resveratrol that reaches targeted tissues but its metabolites, those molecules should be the focus of research in future as a treatment for DS.

5.5 Choline and CoQ10 supplementation

Choline is an essential nutrient that has to be derived from the diet. Although it can be synthesized in the body, this is not sufficient to support bodily needs [105, 106]. Choline supply is critical for brain development because it is a precursor of acetylcholine—a key neurotransmitter for regulating neuronal proliferation, maturation, plasticity, survival, and synapse formation. Besides this, choline is the precursor of phosphatidylcholine and sphingomyelin—principal components of neuronal and other cellular membranes. It is also a primary dietary source of methyl groups in humans [107]. It acts as a methyl donor through the betaine–methionine pathway. Alterations in the dietary levels of choline during early development can produce life-long effects on gene expression through DNA methylation [108].

Disturbances in the cholinergic system are likely due to alterations in acetylcholine metabolism with a significant relationship to AD-like symptoms in DS adults since an impaired acetylcholine metabolism has been reported in the brains of individuals with AD. A reduction in the cholinergic neurotransmitter choline acetyltransferase has also been reported in cortical and sub-cortical regions of DS adult brain tissues [53]. Cholinergic deficits in the brain are a hallmark in humans with DS and Ts16 mice. Brains of DS individuals exhibit a significant reduction in choline acetyltransferase activity in the cerebral cortex, which is consistent with the impaired development of the basal forebrain cholinergic system exhibited by Ts16 mice [109].

So far, there is no evidence that choline supplementation possibly improves cognitive functioning when given to young or adult individuals with DS [110]. On the other hand, several studies proved that perinatal choline supplementation in Ts65Dn mice has beneficial effects on Ts65Dn offspring, including improvements in attention, emotion regulation, spatial memory, and the protection of cholinergic neurons in the medial septal nucleus (MSN) [107, 108, 111]. Specific molecular mechanisms by which supplementing the maternal diet with additional choline exerts life-long effects on offspring functioning are not clear yet, and further studies are necessary [112]. It is believed that it enhances the target-derived neuroprotection of Ts65Dn basal forebrain cholinergic neurons (BFCNs), which typically begin to atrophy at six months of age due to the impaired retrograde transport of nerve growth factor (NGF) [108]. Although Ts65Dn mice do not show all the genetic and phenotypic features of DS, these findings suggest the interesting possibility that increased maternal choline intake during pregnancy may represent a safe and beneficial intervention at the earliest stages [107]. Nevertheless, results obtained in mice tests suggest that current dietary guidelines for choline (425 mg/day for women and450 mg/day for pregnant women) [106], which are necessary to prevent liver damage, may not be sufficient for brain development and higher levels should be taken during pregnancy [110].

Coenzyme Q10 (CoQ10) is lyophilic quinone that can be synthesized by an organism or introduced by the diet. His cell functions include antioxidant activity, carrying

Experimental group	Dosage of CoQ10	Duration of trial	Result	Ref.
30 DS patients	4 mg/kg/day	6 months	CoQ10 treatment was not able to revert DNA damage in heavily compromised cells, while being able to minimize DNA damage in lightly damaged cells.	[114]
17 DS patients 5 to 17 years old	4 mg/kg/day	20 months	Treatment resulted in a significant rise of Co10 in plasma, but it did not affect the overall extent of DNA damage.	[115]
32 DS patients	CoQ10 in a form of ubiquinone (reduced form) in a concentration 4 mg/kg/day	4 years	Long-term treatment did not affect DNA or RNA oxidation in children with DS.	[116]

Table 4.
Examples of CoQ10 supplementation research for DS individuals.

electrons in mitochondria, and serving as a cofactor to some enzymes [113]. There is a theory that CoQ10 could diminish oxidative DNA damage and serve as a therapy for issues related to DS. Research examples presented in **Table 4** show that an additional survey should be conducted in order to confirm this theory.

6. Conclusions

Education and encouragement of caregivers of people with DS to pay attention to the quality of nutrition should be the focus of professionals included in DS rehabilitation. Prevention of nutrient deficiency is certainly cheaper and more effective than dealing with supplementation. Since the metabolic pathways of people with DS are altered, they are more sensitive to nutrient deficiencies than the rest of the population. So, nutrient status should be a part of routine health screening and supplementation should be introduced only after deficiencies of certain nutrients have been identified. Supplementation should be introduced only as directed by a physician. Many research has shown promising results about the improvement of health status and intellectual development of individuals with DS, but the safety of doses and their efficiency have not been proved by independent scientific studies, especially in relation to the diet and nutrient status of DS individuals prior to supplementation.

Conflict of interest

The authors declare no conflict of interest.

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