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Review

Usage of nutritional supplements for individuals with Down syndrome

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Abstract

Down syndrome (DS), as one of the most common genetic disorders, is associated with numerus issues regarding physical and mental development. The introduction of nutritional supplementation in extremely high doses to the everyday routine of individuals with DS is one of the most controversial ideas proposed for the improvement of their physical and intellectual life. Although nutritional supplementation for DS was first proposed in 1940s, it gained popularity during the 1990s. Ever since, an enormous amount of research has become available on the Internet to support this claim, even explaining biochemical pathways relevant for the sustainability of the theory. At the same time, numerous papers which refute this theory and warn of the potential risks have been published, but many of them are not available for the wider population since access to scientific databases is often locked. Thus, parents and caregivers of individuals with DS are left without access to information relevant for their decision-making regarding the usage of supplementation. In this paper, a review of the newest research and conclusions regarding nutritional supplementation in DS is presented.

Key words: trisomy 21, nutritional supplementation, targeted nutritional intervention, oxidative stress

Introduction

Down syndrome (DS) is a neurodevelopmental disorder caused by the trisomy of chromosome 21 (Ts21), first described by Dr. John Langdon Down in 1866. Most cases of trisomy 21 are due to meiotic nondisjunction (95%), usually in the ovum. In the remaining 5% of cases, unbalanced translocation accounts for 3% to 4%, and mosaicism accounts for 1% (1). The natural birth prevalence is between 1:319 and 1:1000 depending on the population and varies with the age of the mother, from 1/2000 in teenage girls to 1/40 in 42-year-old women (2, 3). Malini and Ramachandra (4) point out that although high maternal age is a crucial factor in the birth of children with DS, most children are born from mothers at a younger age. The incidence of births of children with DS depends on sociocultural and religious variables such as the availability of abortions. Every child with DS is unique, and medical conditions associated with DS are not the same for every child. Considering the high rate of healing of conditions associated with DS infants, the mortality rate has fallen from 14.2% to 2.3% (5). The life expectancy among individuals with DS has substantially increased during the last century and is associated with the expansion of governmental and non-governmental initiatives, as well as improvements in medical care and services. Despite these improvements, challenges still exist in implementing health care services for children and adolescents with DS worldwide (6). According to recent research, the average life expectancy of individuals with DS is 60 years. On the basis of life expectancy trends, it is assumed that individuals with DS could live as long as the general population within the next generation (7).

There is an alternative approach to DS which believes that nutritional supplements can lead to the substantial development of the child, which is based on the idea that the extra chromosome causes features associated with DS through metabolic imbalance. Assuming that the phenotypic features and cognitive abilities of individuals with DS can be affected by a variety of supplements, Dr. Henry Turkel developed the first formula in the 1940s. He developed a formulation of 48 different substances called the "U-Series". However, the Food and Drug Administration (FDA) did not approve his request for a new drug because the "U-Series" could not remove impact of the extra chromosome. He got approval for sale only within Michigan State. A modified application of Turkel's supplements was developed by Dr. Jack Warner during the 1980s and was called High Achievement Potential Capsules (HAP Caps) which contained a high dosage of dietary antioxidants such as vitamin A, E and C, digestive enzymes, minerals zinc (Zn), copper (Cu), manganese (Mn) and selenium (Se), which help with metabolic disturbances. HAP Caps were formulated in an FDA laboratory and received their approval from 1986 until his death in 2004 (8, 9).

In the early 1990s, Dixie Lawrence Tafoya adopted elements of both treatments and added new factors to create a Targeted Nutritional Intervention (TNI). Besides different nutrients, TNI also includes amino acids and smart drugs (Piracetam). An early intervention strategy (even at the prenatal stage) is one of the main concepts of this program. In 1996, she promoted a formula called Nutrivene-D, manufactured by International Nutrition Inc. in the USA, and set up a non-profit company called Trisomy 21 Research Foundation with a "Scientific Advisory Committee". At the same time, in Canada, Nutrichem Laboratories, under the guidance of Kent Macleod, marketed a supplement similar to Nutrivene called "MSB Plus", in accordance with Good Manufacturing Practices standards in a licensed Health Canada Site facility.

Although various supplements have been applied to children with DS since the 1950s, repeated studies have shown that there are no nutritional deficiencies common to all children with DS, and no study has ever documented the need for any of these supplements, with the possible exception of the minerals Zn and Se (9, 10).

Despite the clear scientific warnings of there being controversial and doubtful results of nutritional supplementation (11), its usage is still very popular. In this paper we search the literature for the latest findings and opinions in this field.

Previous observations on nutritional supplementation in DS

During the 1980s and especially 1990s, nutritional supplementation for DS gained huge popularity. This resulted in the overproduction of scientific reports which tried to explain the biochemical pathways and the consequential influence on DS features and a possible solution for related issues. At the time, several reviews which tried to cover published findings have been issued. Sacks and Buckley (9) reviewed supplementation theories and issues related to it. First of all, they highlighted that it is not true that individuals with DS are deficient in certain nutrients. Actually, if they consume a well-balanced diet and have no additional medical problems, they probably receive the recommended daily allowance (RDA) from an ordinary diet. Thus, all supplements taken should be considered as additional to average intake. They also warned of the lack of well-designed scientific studies. Datta and Vitolins (12) concluded that there is no simple solution for implementing supplementation to everyday routine because there are different eating patterns and nutrient needs of population. One of the major concerns is the lack of studies on the effects of long-term nutritional supplementation. Ani, Grantham-McGregor, and Muller (13) and Roizen (14) clearly stated that the majority of studies which support supplementation have major methodological shortcomings in the sense of small samples, the wide age range of participants, short duration, and very few randomized controlled and blinded trials. Leshin (15) warned of misrepresenting the nature of DS in some promotional literature as a "progressive degenerative disease that if left untreated would lead to poor health, mental retardation and premature death". He stated that there is no evidence that any nutritional supplement enhances the prognosis, but many parents perceive these treatments as therapies which cannot hurt and might help, which

is also not true. Blair et al. (16) could not relate the decrease of risk of acute lymphoblastic leukemia and childhood vitamin use, but warned of the increased risk of acute myeloid leukemia among children who begin taking vitamins during their first year of life or take them for a long duration.

The popularity of nutritional supplementation in recent years was confirmed by Lewanda, Gallegos, and Summar (17). They conducted a survey among 1200 respondents in USA, Brazil and the EU. They found that almost half of pediatric patients with DS use or used nutritional supplementation. Many children started to use these supplements in extremely young age. About 20% of parents who give their child nutritional supplements have not informed their pediatrician. They also observed that some commercially available products contain vitamins in a dosage which far exceeds FDA recommendations. Vitamin E is 5000% of the daily value for children under age 4, and 1670% of the daily value for those older than 4 years, which is similar to other fat-soluble vitamins which are stored in the body with uncertain long-term consequences.

Theoretical aspects of oxidative stress in individuals with DS

Oxidative stress theory was developed in the 1950s as a result of X-irradiation studies, but it led to the findings that oxygen radicals, called reactive oxygen species (ROS), are normally formed during oxidative metabolism. ROS include free radical superoxide ($O_2^{\bullet-}$), hydroxyl ($OH^{\bullet}$) species and other molecules such as hydrogen peroxide (H_2O_2) and peroxynitrite which have the ability to become highly damaging to cells. Consequently, cells develop different mechanisms in order to eliminate ROS, free radicals and reactive metabolites; they are usually neutralized by antioxidant enzymes (superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT)) and antioxidants such as vitamins C, E or glutathione. In the case of the excessive production of oxidants, the ability of cells to eliminate them fails and oxidative stress occurs. A constant balance between oxidants and the antioxidant ability of the cell is part of the normal cell function (18, 19).

Oxidative stress hypothesis has been recognized as a possible explanation for numerous issues associated with DS, such as intellectual disability, accelerated aging, cognitive and neuronal dysfunction (13, 20-22). A great number of studies have been carried out in order to confirm increased oxidative stress in DS (Table 1) and identify mechanisms responsible for the clinical phenotype and intellectual disability. Besides those already mentioned, there is a close relationship between DS and a dementia syndrome, similar to Alzheimer's disease, which occurs in almost all individuals with DS over the age of 40. Zana et al. (31) claim that the prevalence of dementia among DS patients is 8% in the age range 35–49, 55% in the age range 50–59, and 75% above the age of 60 years. A part of the long arm of chromosome 21 represents the DS critical region (DSCR). The overexpression of genes in DSCR and consequent down or up-regulation of their targets have been proposed as a cause of DS features. The excessive synthesis of multiple gene products derived from the overexpression of the genes present on chromosome 21 is thought to underlie both dysmorphic features and the pathogenesis of the neurological, immunologic, endocrine and biochemical abnormalities that are characteristic of DS (21, 32, 33). The overexpression of the encoded proteins leads to the overconsumption of their substrates and overproduction of their metabolic end-products. Among others, superoxide dismutase 1 (SOD1), which is involved in the regulation of redox homeostasis, is part of DSCR (34).

The enzyme SOD occurs in the body in three isoforms: (1) Cu/Zn SOD, an intracellular dimeric enzyme containing Cu and Zn ions in the active center (SOD1); (2) extracellular Cu/Zn SOD, which has the same ions in the active center but different tetrameric apo-enzymes; and (3) mitochondrial, also tetrameric, Mn SOD (SOD2), containing an Mn ion in the active center (35). SOD1 is the gene encoding for the enzyme Cu/Zn SOD that catalyzes the conversion of O_2^- into H_2O_2 in the cytosol. The increase in SOD activity results in the formation of elevated levels of H_2O_2. It can be efficiently removed by other enzymes such as CAT, GPx and thioredoxin peroxidase. In the case of DS, elevated levels of H_2O_2 are not compensated by an elevation of CAT and GPx, which results in the overproduction of ROS (27, 36-38).

Table 1. Examples of oxidative stress in DS research.

Participants	Evaluated parameters	Results	Conclusion	Reference
30 patients with DS, 14-24 Y, both genders; 30 healthy subjects, mached by age to DS, both genders.	activity of salivary peroxidase, activity of salivary superoxide dismutase (SOD), salivary uric acid, salivary ascorbic acid, total antioxidant capacity of saliva, malondialdehyde, carbolnylated proteins and total protein content	Higher concentrations of SOD, malondialdehyde and total proteins in DS patients. No difference in carbonylated proteins, uric acid, ascorbic acid, peroxidase activity and total antioxidant capacity.	DS patients are more vulnerable to oxidative stress in saliva.	de Sousa et al. (23)
50 patients with DS, 3-24 Y, both genders; 50 heathy subjects, mached by age to DS, both genders.	serum thiobarbituric acid reactive substances (TBARS), serum SOD activity, serum catalase (CAT) activity, uric acid levels, total serum iron, total iron-binding capacity (TIBC), erythrocyte osmotic fragility, hemograms	Higher levels of TBARS, uric acid, SOD and CAT activity in DS subjects. No difference between groups in total serum iron, TIBC and hemograms.	Increased oxidative stress in individuals with DS.	Garcez et al. (24)
21 patients with DS, average age 6.7±3.0 Y, both genders; 18 healthy subjects, average age 7.7±3.8 Y, both genders.	blood catalase (CAT), SOD, glutathione reductase (GR) and glutathione peroxidase (GPx) activity, gamma-glutamyl transferase (GGT) activity, glucose-6-phosphate dehydrogenase (G6PD)activities, myeloperoxidase (MPO) assay, reduced glutathione (GSH) assay, serum uric acid (UA), plasma vitamin E, plasma TBARS levels, plasma protein carbonyls	Elevated SOD, CAT, GR, GGT and MPO activities, increased uric acid levels, no difference between groups in PPx, G6PD, vitamin E levels and TBARS levels.	Increased oxidative stress in individuals with DS.	Parisotto et al. (25)
3 fetuses with DS; 3 fetuses as controls.	SOD activity, CAT activity, GPx activity, oxidized and reduced glutathione ratio (GSSG/GSH ratio), peroxide levels, cellular proliferation assay, analysis of apoptotic cells	Proliferation of fibroblasts from DS fetuses was lower compared to controls, higher peroxide levels in DS fetuses, higher GSSG/GSH ratio in fibroblasts from DS fetuses increased SOD, decreased GPx activities.	Increased oxidative stress in fetuses with DS.	Gimeno et al. (26)
Unlisted number of subjects with DS, mostly from 6-10 Y, both genders; 18 healthy children, 3-12 Y, both genders.	blood CAT, SOD, GR, GPx, glutathione transferase (GST) activities, GSH assay, serum uric acid, vitamin E, plasma TBARS levels, protein carbonyls (PC)	Increased activities of SOD, CAT, GR in DS subjects compared to controls, no difference in GPx activity, TBARS and vitamin E levels, decreased activity of GST and decreased PC levels compared to controls.	Systemic pro-oxidant status in DS children.	Garlet et al. (27)

Participants	Evaluated parameters	Results	Conclusion	Reference
78 subjects with DS; 65 healthy controls. Three age groups for DS and control subjects: 15-19 Y, 20-40 Y, > 40 Y.	urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG), isoprostane 15-F_{2t}-IsoP, TBARS, advanced glycation end products (AGEs), dityrosine (diTyr), H_2O_2, nitrite/nitrate (NO_x)	No difference in 8-OHdG and AGEs for any age group. 15-F_{2t}-IsoP and TBARS levels were lower in DS than in controls for age group 3, both biomarkers correlated negatively with age in DS. Significantly higher levels of diTyr in DS subjects than in controls. Higher levels of H_2O_2 and NO_x in DS patients for age group 15-40 Y with large individual variations.	AGEs, diTyr, H_2O_2 and NO_x proved oxidative stress in DS subjects.	Campos et al. (28)
26 children with DS; 19 control healthy subjects, biological siblings to DS subjects. Two age groups for DS and control subjects: < 10 Y and ≥10 Y.	8-OHdG, isoprostane 15-F_{2t}-IsoP, TBARS, AGEs, diTyr, H_2O_2, NO_x	No difference between DS and control groups in 8-OHdG, 15-F_{2t}-IsoP, TBARS, AGEs, H_2O_2 and NO_x. Increased level of diTyr in DS children compared to their control siblings in case when DS subjects have hypothyroidism.	Oxidative stress cannot be explained by urinary levels of measured parameters.	Campos et al. (29)
48 individuals with DS aged 2-52 Y; 130 controls aged 4-78 Y for allantoin parameter; 85 controls aged 4-75 for 2,3-dinor-iPF2α-III parameter.	urinary allantoin and 2,3-dinor-iPF2α-III	DS subjects did not exhibit increased levels of measured biomarkers.	Chronic systemic oxidative stress in DS subjects is not proved.	Tolun et al. (30)

SOD1 was found in levels 50% higher than normal in a variety of cells and tissues of individuals with DS, and so the SOD1/GPx activity ratio is consequently altered (20, 27, 39-41). Several authors demonstrated that fetal DS neurons generate increased levels of ROS, leading to neuronal apoptosis, which may contribute to abnormal brain development and intellectual disability (42, 43). The accumulation of highly diffusible and relatively stable endogenous H_2O_2 is able to generate other deleterious ROS through the Haber–Weiss–Fenton reactions, which damage important cellular components by oxidizing biomolecules such as amino acid residues, proteins, lipids and DNA (27, 44).

Garlet et al. (27) performed a study on 20 participants with DS in the age group of 6–10 and in a control group of 18 children without DS aged from 3 to 12. There was no significant difference in the body mass index between the two groups. SOD, glutathione reductase (GR) and CAT activity in individuals with DS showed increased values compared to the control group. On the other hand, GPx activity in DS patients showed no significant difference compared to controls.

Strydom et al. (45) studied the hypothesis that an increased SOD1/GPx ratio would be associated with poorer ability on a cognitive test. The study included 32 adults with DS (age 18 to 45) but the hypothesis was not supported. However, they found that a high SOD1/GPx ratio was associated with worse memory ability. The possible explanation for this included other factors which also influence SOD1 or GPx activity such as regular exercise (GPx increases with exercise), Se levels (increased Se level increases GPx activity) and higher homocysteine levels (associated with poorer cognitive ability in DS).

The results of Pallardó et al. (46) point to the occurrence of an early *in vivo* pro-oxidant state in DS patients and its relation to a number of consequences in the DS phenotype (as previously mentioned). In order to evaluate this, they measured leukocyte 8-hydroxy-2'-deoxyguanosine, blood glutathione, plasma levels of glyoxal and methylglyoxal antioxidants (uric acid, ascorbic acid, and vitamin E) and xanthine oxidase activity in a group of 32 DS patients aged from 2 months to 57 years. They also included 63 control healthy patients. The results showed significantly higher levels of leukocyte 8-hydroxy-2'-deoxyguanosine, uric acid, ascorbic acid and increased xanthine oxidase activity in DS patients compared to control donors of all age groups. No significant differences among glutathione levels and vitamin E have been observed. Glyoxal and methylglyoxal levels showed a significant decrease in 23 DS patients compared to 23 controls. The authors suggested the future clinical management of DS patients in order to foresee the need for pharmacological and/or nutritional interventions in DS patients since the earliest life stages.

Although the imbalance of redox homeostasis has been undoubtedly proved, some authors point out that it cannot be explained only by the SOD1 gene dosage effect (47, 48). Besides, Pastore et al. (49) failed to prove systemic oxidative stress despite the observation of glutathione homeostasis imbalance.

Therefore, research on diminishing oxidative stress and related effects is still a focus of scientists. Here is a review of some attempts in this area.

Vitamins as antioxidants

The usage of supplementation with single or vitamin mixtures has been researched in numerous studies. As already mentioned, it is believed that individuals with DS have a high predisposition to oxidative stress as a result of elevated production of H_2O_2. It is known that proteins, lipids and DNA are very liable to oxidation (21). Since individuals with DS have elevated levels of DNA damage and lipid peroxidation, a pro-oxidant state is present early in life (50). Vitamin E is the common name for the group of several fat-soluble compounds, among which α-tocopherol is the most important (51). The primary role of vitamin E is the prevention of oxidative stress. It is a potent chain-breaking antioxidant that inhibits the production of ROS when fat undergoes oxidation and during the propagation of free radical reactions. α-tocopherol mainly inhibits the production of new free radicals, while γ-tocopherol traps and neutralizes already existing free radicals. So, a mixture of tocopherols exhibits a stronger inhibitory effect compared to α-tocopherol alone (52). This is particularly important for the prevention of oxidative stress in multi unsaturated fatty acids present in the membrane structures of cells. Recently, its role in mental disorders was determined; it was shown that vitamin E plays a key role in normal mental functioning in humans (51).

Some authors suggest a possible favourable impact of antioxidant vitamins on cognitive decline in DS, but randomized, controlled trials are required for confirmation (53, 54). The resistance of cells to oxidative stress is associated with a sufficient antioxidant status especially of glutathione, ascorbic acid and vitamin E—the factors that protect against oxygen radical damage. The study performed by Sulthana et al. (55) included 31 children with DS and an equal number of matched controls to prove the claim that levels of erythrocytic reduced glutathione and plasma total antioxidant status were significantly reduced in children with DS. They concluded that children with DS have elevated levels of oxidative stress and that antioxidant therapy could be beneficial for them. Vitamin E treatment is assumed to have a protective effect on chromosomal injury in individuals with DS through an antioxidative mechanism in lymphocytes, reinforcing the presumption of oxidative stress. A large randomized placebo-controlled study on 20,536 individuals who used a supplementation of 600 mg/day of vitamin E, 250 mg/day of vitamin C and 20 mg/day of carotene did not exert any influence on cognitive impairment (56).

During middle age, individuals with DS develop the characteristic neuropathology of Alzheimer's disease, including amyloid plaques, the progressive degeneration of basal forebrain cholinergic neurons and cognitive deterioration consistent with Alzheimer's type dementia (50, 57). Both DS and Alzheimer's disease individuals share a high susceptibility to oxidative stress, so there has been numerous studies on

both groups with the aim of decreasing oxidative damage and causing cognition improvement.

It is believed that the knowledge gained in DS mouse models provides a rational basis to start new clinical trials in infants, children and adults with DS, exploiting drugs that have proved able to rescue various facets of the DS neurologic phenotype (58). Many studies focused on oxidative stress involve the monitoring of changes on Ts65Dn mice and Ts1Cje mice (59, 60). Ts65Dn mice have a cerebellar pathology with direct parallels to DS because they carry a small chromosome derived primarily from mouse chromosome 16 which causes a dosage imbalance orthologous to approximately half of human chromosome 21 (61). Shortly, oxidative stress is increased and respiration is decreased in trisomy 16 mouse models for DS (62).

The study performed by Lockrow et al. (50) in mouse models gave promising results for vitamin E usage. They found a strong correlation between oxidative stress and working memory decline in Ts65Dn mice. The efficacy with which vitamin E was able to improve neuronal and oxidative stress markers in Ts65Dn mice suggests that the dietary intake of vitamin E may be sufficient to counteract the increased oxidative stress that was observed in this particular mouse model and may be generalized to neurodegenerative diseases such as DS and Alzheimer's disease in humans. The authors also point out that transgenic mice could be a useful model to study the molecular basis of a disease and test the efficacy of drug treatment, but the fact that mice do not show all the features of human disease must be taken into account. Zmijewski et al. (63) presented results of research in which omega-3 containing fish oil with other healthy nutraceuticals can modestly suppress regulator of calcineurin 1 (RCAN 1) levels in mice and supported the idea that fish oil could be an effective and cheap agent to treat genetically defined pathologies. It is very important to mention that, at this point, it is not known whether the developmental delays and intellectual disabilities seen in DS children are caused by the same genes that induce cognitive deterioration in DS adults. Studies which exhibited no efficacy in improving cognitive development in DS indicate that there are differing etiologies between the early pathology seen in children and DS dementia in adulthood, or may indicate the limitations of vitamin E as therapy. It is also important to say that DS has an earlier onset compared to Alzheimer's disease. It is believed that, in DS, the systemic oxidative stress from elevated SOD activity is so high that mitochondrial performance is already compromised at birth. In Alzheimer's disease, the genetic burden is not present, and time is relevant for cumulative oxidative influences to initiate and drive degenerative progression (64). Lockrow et al. (50) concluded that vitamin E supplementation may show benefits in younger individuals as preventive therapy, but it requires additional clinical trials. On the other hand, Tanabe et al. (65) could not provide any evidence that elevated Cu,Zn–SOD activity affected the vitamin E status in DS, particularly the cellular level of vitamin E.

An interesting finding was provided by Nachvak et al. (22): they measured thiobarbituric acid reactive substances (TBARS) which consist mostly of malondialdehyde (MDA) in serum and 8-hydroxy-2-deoxyguanosine (8-OHdG) in urine as markers of oxidative stress. They observed higher urinary 8-OHdG concentrations in DS boys than in DS girls, which suggests that males with DS are more vulnerable to oxidative damage. The clinical significance of this effect is uncertain, because there is no suggestion that symptom severity is increased in DS boys. Nevertheless, TBARS levels were not significantly affected by antioxidant intervention, but 8-OHdG levels were significantly reduced by α-tocopherol intervention at a level of 400 IU per day. This research supports the idea that the potential dosage of 400 IU is safe and still could have a potential impact on cognitive development in DS children.

Vitamin C is an essential micronutrient required to maintain physiological functions and the integrity of an organism; humans cannot synthetize it and depend on a continuous exogenous supply. It is cofactor for several enzymes involved in the biosynthesis of collagen, carnitine and neurotransmitters, but the main biological function is that it acts as a water-soluble antioxidant (66). Vitamin E is strongly dependent on vitamin C, B3, selenium and glutathione. A cooperative interaction between vitamin C and vitamin E is quite probable (52). The combination of α-tocopherol and ascorbic acid is often used because of the theory

that ascorbic acid helps to stabilize the concentration of α-tocopherol in plasma. It has a role in the protection of other vitamins (especially vitamin A and E) from the harmful effect of oxidation by regenerating them to their active state (51, 67). As an antioxidant, vitamin C reacts with other compounds such as histamines and peroxides to reduce inflammatory symptoms (68), and it protects lipids, proteins and DNA molecules (69).

Lott et al. (57) could not observe any clinical improvement or stabilization of dementia in 53 individuals with DS after usage of 900 IU of α-tocopherol together with 200 mg of ascorbic acid and 600 mg of α-lipoic acid in 2 years of a randomized double-blind study. The authors point out that a possible reason for the lack of observed efficacy may relate to the combination of antioxidants used or the dosage of individual antioxidants. After all, the authors suggest that, in future studies, the usage of antioxidants could be applied at a younger age, since in this particular study, the average age of participants was 50 years. In that light, a study provided by Zandi et al. (70) examined the relationship between antioxidant supplementation and the risk of Alzheimer's disease. They included a large sample of participants with various combinations of vitamin usage. The combination of vitamins E and C gave positive results in the sense of a reduced prevalence and incidence of Alzheimer's disease, while the use of those vitamins alone did not exhibit any positive effect. The authors also point out the weakness of the study considering the fact that the follow-up period (3 years) was relatively short. An important issue when using supplements is the dosage. Binns et al. (71) warn that the usage of supplements brings many risks including organ damage, interactions, potential toxicity, and above all some individuals believe that supplements have benefits comparable to a healthy diet. 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. Harrison (19) reviewed many studies about the influence of vitamin C (alone or in combination with vitamin E); some of them support and some of them do not support increased vitamin C intakes in relation to cognitive decline in Alzheimer's disease. However, perhaps the most important observation was that in many cases there is a strong correlation between a low intake of fruit and vegetables and bad cognitive function. Thus, it can be concluded that the prevention of deficiency is potentially more important than above-normal supplementation.

Supplementation with antioxidant vitamins (vitamin E 100 mg, vitamin C 50 mg, vitamin A 0,9 mg) together with antioxidant minerals (Se 10 μg, Zn 5 mg) and with or without folinic acid (0,1 mg) for DS children was investigated by Ellis et al. (40). They could not prove a significant effect of antioxidant and/or folinic acid supplementation on SOD activity, GPx activity or the SOD/GPx ratio. They pointed out that the doses used were in accordance with RDA values and much lower than in some commercially available preparations. They also highlighted that side effects of higher-dose preparations used over a long period are actually unknown and potentially associated with increased mortality across a range of conditions. Kurutas (72) and Landete (11) expressed concerns regarding antioxidant supplementation since removal of to many reactive oxygen species could actually disturb cell signalling pathways and increase the risk of chronic diseases. Therefore, vitamin supplements shouldn't exceed RDA values.

Parisotto et al. (25) demonstrated the effect of a six-month period of oral antioxidant supplementation (400 mg vitamin E and 500 mg vitamin C) on 21 DS children and 18 healthy children without DS as a control group. Results showed higher erythrocytic SOD (47%) and CAT (24.7%) activity in DS children compared to controls. The observed elevation was decreased by vitamin supplementation to values similar to those found in controls. Antioxidant intervention caused decreased activity of GPx (46%) in DS children, but not in the control group. The authors proposed that further studies are necessary to clarify the possible neurological benefits of such supplementation.

Lott (73) in his review article concluded that, despite strong animal evidence for oxidative stress, clinical trials for antioxidant usage did not give satisfactory results. The author also suggested the possibility of antioxidant usage during early intervention, before dementia occurs. Since it is not proven that the

existing combinations of antioxidants actually prevent dementia and relieve its symptoms, the author considers it necessary to conduct research in the direction of the application of new antioxidants through a new approach.

Another theory says that deficiency of B group vitamins can be a cause of dementia in individuals with DS through the metabolism of homocysteine, which requires cofactors such as vitamin B6, B12 and folic acid. An accumulation of homocysteine may result from changes in its metabolism, a deficiency of B vitamins or a malfunction of the enzymes involved in its metabolic pathway. Homocysteine is cytotoxic and is usually transported out of cells into the plasma, so high plasma levels of homocysteine reflect high intracellular concentrations (74, 75). However, it is proved that the plasma homocysteine concentration in individuals with DS is increased, probably by a gene overexpression on chromosome 21. Supplementation with folic acid (5 mg/day), alone or combined with vitamin B6 (5 mg/day) or B12 (100 g/day) or both, was able to decrease the plasma homocysteine level in individuals with DS (13).

Several authors also confirmed a positive impact of folic acid, vitamin B2, B6, and B12 supplementation on the reduction of homocysteine levels. They showed that the consumption of high doses of mentioned B group vitamins slowed the rate of accelerated brain atrophy in subjects affected by mild cognitive impairment (76-79).

The efficacy of combined folic acid, B6, and B12 vitamin supplementation to reduce homocysteine is well documented, but sometimes it is difficult to determine who can really benefit from it since research show controversial results (80). Fillon-Emery et al. (81) reported that folic acid supplementation is considered as a treatment for the prevention of functional folate deficiency in DS. Although the use of folinic acid or antioxidants in DS patients is not supported by scientific evidence and does not provide any improvement in cognitive performance to patients (82), many parents or guardians of individuals with DS are influenced by promotion of B group vitamins as "correctors of metabolic pathways that have gone wrong as the result of the extra chromosome 21" (81). However, research performed by Fillon-Emery et al. (81) showed that the plasma homocysteine concentration of individuals with DS who did not take supplemental vitamins was not significantly different from that of controls. There were also no significant difference between nonusers and controls in red blood cells folate, serum folate, or serum vitamin B12.

Minerals as antioxidants

During the 1980s and 1990s, different theories of reducing oxidative stress were researched. The application of some minerals, primarily Se and Zn, is among them. This theory is based in the fact that GPx, an important enzyme in redox homeostasis of the cells, is an Se-containing enzyme, while SOD is a Cu and Zn-containing enzyme. GPx belongs to the selenoprotein family, a group of proteins that contains selenocysteine (the 21st amino acid), a form of Se (83, 84). GPx in humans exists in eight isoforms, of which five are Se-containing: GPx1 (cellular GPx), GPx2 (intestinal GPx), GPx3 (plasma GPx), GPx4 (phospholipid GPx) and GPx6 (85). The GPx enzymes utilize Se at their active sites to detoxify ROS including H_2O_2 and phospholipid hydroperoxide. GPx1 and GPx4 are expressed in most tissues (84). Therefore, Se is considered one of the antioxidant nutrients and has interdependent roles with vitamin E, iron (as CAT), Zn and Cu (as SOD) (83). One of the early research works by Nève et al. (86) investigated the plasma levels of the mentioned minerals. They showed that the mean plasma Zn level of DS subjects was not different from that of a control group, although low and high levels sporadically occur. A similar result was obtained for Cu, but mean plasma Se was significantly decreased in DS subjects. Of course, they highlighted the importance of the evaluation of Se intake, since they only assumed that both groups were in similar environmental conditions (neither of the participants were institutionalized or hospitalized). Erythrocyte Se was, on the other hand, identical in the two groups, although the activity of GPx was significantly increased in the DS group. This can be explained by the fact that Se, as part of the GPx enzyme, is only 10% of total red cell Se. Such results stimulated interest in further research. Antila et al. (87) introduced Se supplementation as Na–selenite in a dose of 0.015–0.025 mg/kg/day in

period of 0.3 to 1.5 years. GPx activity increased by 25% and the SOD1/GPx ratio decreased by 23.9% in the Se group. It has to be pointed out that this research included a highly non-homogenous group aged 1 to 54 years, so all future research about the potential influence of decreased SOD1/GPx ratio on cognitive skills should be on a homogenous group of subjects.

Meguid et al. (88) found that Se is at insufficient concentrations in individuals with DS. They studied the activities of SOD and GPx, as well as the levels of their cofactors Cu, Zn and Se. The research included 18 DS children aged from 8 months to 3 years with trisomy 21, translocations, and mosaicism and control group of 15 children. Results showed that plasma Cu levels were significantly increased in all three DS groups, and the plasma Zn concentrations were normal. On the other hand, whole-blood Se levels were decreased significantly in all patients compared to controls, with no correlation between whole Se levels and GPx activity. They also reported that both SOD and GPx activity do not show a correlation with clinical manifestations of DS or the various developmental fields. Therefore, the authors proposed future investigations of lipid peroxidation or mitochondrial DNA repair mechanisms which may clarify the pathogenesis of the clinical manifestations in individuals with DS, which is still unknown.

It is also hypothesized that Se supplementation has a positive influence on serum concentrations of IgG2 and IgG4 in children with DS. DS children are known to be very susceptible to bacterial respiratory infections, and IgG2 is believed to be a part of the immune response to bacterial antigens. Although Se deficiency is uncommon among the general population, decreased Se concentrations have been found in patients with severe bacterial infections (89).

Besides this, Se is crucial for the production of proper thyroid hormone levels. The thyroid gland is characterized by a high tissue concentration of Se, as the organ with the highest amount of Se per gram of tissue, because it contains most of the selenoproteins. Being incorporated into iodothyronine deiodinase (type 1, 2 and 3), Se plays important role in the metabolism of thyroid hormones (84, 90). The role of selenium in thyroid function is in direct relation to oxidative stress issues. The alteration of the defense mechanisms (used to fight the oxidative stress) related to selenium deficiency results in the aberrant iodination of certain proteins, leading to cell apoptosis or the exposure of unusual epitopes possibly recognized by the immune system. Apoptosis is induced by high doses of H_2O_2, while the preincubation of human thyroid follicles *in vitro* with low doses of selenium increases GPx activity and reduces cell death (91). When Se intake is adequate, the intracellular GPx and thyroide systems protect the thyrocyte from peroxides and decrease oxidative damage (39).

Individuals with DS are at an increased risk of hypothyroidism, so Se supplementation may be helpful for those with DS (92). Adequate nutrition should also be taken into account when considering proper Se levels in the general population and in individuals with DS, especially since the latter are known to have low Se and Zn levels. Proteinaceous foods (meat, fish, shellfish, eggs, cereals) are richest in selenium, but the bioavailability of the selenium they contain is variable (20%–50% for seafood and more than 80% for cereals and brewer's yeast). Besides this, the selenium content in cereals is dependent on content of the soil where they are grown (much lower in Europe compared to North America). Selenomethionine has been identified as a major component of cereals, yeasts and meat, while inorganic selenium (sodium selenite, selenite) has been identified in drinking water in small amounts, and is also used in food supplements because of its excellent bioavailability (91, 93). Reduced Se levels are found in smokers, decrease with age and are also associated with the consumption of eggs, white rice, alcohol and coffee (90).

Zn plasma deficiency is also related to DS (94). Zn is essential for the function of numerous enzymes and transcription factors. In the normal brain, Zn is bound to membrane-bound metallo-proteins, or loosely bound within the cytoplasm to proteins and enzymes as well as being in synaptic vesicles that are enriched with Zn. So, a change in the homeostasis of Zn can have an impact on learning and memory, although role of Zn in cognitive functioning is not clear yet. Zn metabolism is suggested to play a major role in many processes related to brain ageing and the development of age-related neurodegenerative diseases (95, 96). Zinc transporters (ZnT) are also crucial

to maintain memory and cognitive function. Although certain ZnT are connected to manifestations of Alzheimer's disease, a role of ZnT is not clearly investigated in DS (97). Besides being a part of a Cu–Zn SOD, it helps protect cells and compounds from the harmful effect of free radicals. It is also considered as one of the most important nutrients of the immune system as an antioxidant and an anti-inflammatory agent because it is necessary for the formation of antibodies, leucocytes, thyroid glands and hormones (51, 98). Haase et al. (99) indicated that Zn has several positive effects on individuals with DS such as the normalization of thymulin levels, thyroid hormones and functions of a several immune cells. Zn stabilizes the 3-D structure of SOD enzyme. It has also been shown by some studies that Zn metabolism is altered in the presence of DS, and deficiency in this trace element in plasma is associated with metabolic alterations usually present in DS (100). They also observed decreased Zn levels in the plasma of DS subjects in comparison to the control group. On the other hand, erythrocyte Zn levels were adequate and above (74% and 17%, respectively) the recommended range in the DS group. This could be explained by several facts: a reduced plasma Zn concentration may be a result of a redistribution of a mineral in organism, not necessarily an inhibition of its absorption. High level of erythrocytes Zn could be a result of increased Cu–Zn SOD activity. In the end, if DS children are iron deficient (which occurs quite often), Zn binds to the protoporphyrin instead of the iron. At the same time, Cocchi et al. (101) observed that, at up to 5 years of age, plasma Zn levels are actually adequate, but tend to decrease after this age. Decreased hair Zn levels were also observed by Yenigun et al. (102), but the authors highlighted the important fact that food habits and frequency of intake of different products also influence Zn concentrations in hair. An early study implied that Zn supplementation can influence growth hormone (103). Stabile et al. (104) also observed low plasma Zn levels in DS patients, but no correlation was found between the Zn deficiency and the recurrence or intensity of infections. Besides this, the absolute number of peripheral lymphocytes, the percentage of B lymphocytes, and serum IgG, IgA and IgM levels did not differ between studied DS children and the control group. They also observed that only some DS children exhibited low serum Zn levels, and after oral Zn supplementation, there was an increase in serum Zn concentration and improvement of lymphocyte proliferative response. Yengun et al. (102) highlighted variant results regarding Zn deficiency and its influence on the biochemical and health status of DS children. In the end, there were no significant differences regarding growth hormone secretion, IgA and IgG antibodies, thyroid function and total immunoglobulins between DS children with normal and low Zn levels. More recent research points out that the immune dysfunction of individuals with DS is very complex and probably deficient from the very beginning and not simply a result of a generalized process of precocious ageing induced by oxidative stress (105, 106).

Polyphenol antioxidants

Mitochondria represent the main source of energy production, consuming about 90% of mammalian oxygen to generate adenosine triphosphate (ATP) via oxidative phosphorylation (OXPHOS). The oxidation reaction involves the donation of electrons to the mitochondrial electron transport chain in the mitochondrial inner membrane. The mitochondrial phenotype in DS is characterized by a reduced efficiency in producing ATP through OXPHOS, a decreased respiratory capacity and ability to generate mitochondrial membrane potential. Mitochondrial dysfunction is proposed to be an inherent feature of DS. As previously mentioned, individuals with DS are prone to oxidative stress because of increased SOD1 expression. Besides this, Hsa21 amyloid-β precursor protein (APP) is believed to be another player involved in the origin of oxidative stress and in brain damage in DS patients.

The association between oxidative stress and mitochondrial dysfunction is relevant since the mitochondria is the major site for free radical generation and the main target of ROS. It can be concluded that mitochondrial alterations principally affect the brain, which is highly vulnerable to energy deficit and susceptible to oxidative stress (34).

Green tea contains a number of bioactive chemicals including catechins and their derivatives (107).

Epigallocatechin gallate (EGCG) is the most abundant catechin present in green tea. It is considered as ten times more effective as a free radical scavenger than vitamin E or C. EGCG can readily cross the blood–brain barrier, making it an attractive compound for therapy. Unfortunately, it is considered that the bioavailability of polyphenols (including EGCG) is poor because of their poor absorption, rapid metabolism and excretion. They undergo extensive enzymatic modification and are normally conjugated in the intestinal cells and later in the liver in order to be eliminated from the organism (108). Still, many *in vivo* trials are needed to clarify whether EGCG and its metabolites can reach the brain at sufficient concentrations, alter cell signalling pathways after peripheral injection, and thereby affect the progression of neurodegeneration (13, 109).

Proposed mechanisms of EGCG mitochondrial action are the result of studies carried out in mouse and cell models: (1) it acts as a ROS scavenging agent, (2) protects against β-amyloid induced mitochondrial apoptosis, (3) protects against glutamate cytotoxicity and (4) activates mitochondrial bioenergetics and biogenesis. Besides this, EGCG exhibits the activation of activated protein kinase (AMPK) which results in increased ATP synthesis, influences phosphorylation/acetylation status (specially in mitochondrial complex I), influences the activity of peroxisome proliferator-activated receptor-y coactivator 1 alpha (PGC-1α), and promotes respiratory chain function and neural progenitor cell proliferation (34, 108).

It is very important to highlight that, in high doses EGCG, actually functions as a prooxidant and is harmful to skeletal DS phenotypes. A dosage of 10 mg/kg/day in combination with fish oil has been observed as safe for humans, with a beneficial effect on mitochondrial dysfunction and behavioral deficits (case study on a 10-year-old DS child) (110). On the other hand, doses above 10 mg/kg/day—up to 50 mg/kg/day—are considered as harmful without any positive effect on a Ts65Dn mouse model (111). Advocates of EGCG supplementation highlight that polyphenols found in food are in lower concentrations compared to their effective dose in humans. So, it is suggested that novel EGCG analogs could have the potential for increased bioavailability and efficacy against neurodegenerative processes. Although studies in mouse models gave promising results (111), *in vivo* studies in human are yet to be done.

It is also believed that EGCG present in green tea inhibits the activity of kinase DYRK1A (dual-specificity tyrosine phosphorylation regulated kinase 1A), a gene located on chromosome 21 for which it is assumed that its increased expression is associated with the cognitive deficits and learning disability characteristic for individuals with DS. Three copies of DYRK1A have been hypothesized to lead to cognitive and skeletal deficits associated with Ts21. The subtraction of one copy of DYRK1A in otherwise trisomic DS mouse models improved cognitive, neurological, and skeletal deficits. Thus, trisomic DYRK1A has been recognized as a rational target for therapeutic drug treatments (112). De la Torre and Dierssen (82) highlighted that many clinical trials which intended to evaluate the therapeutic efficacy of different therapies in DS patients suffer from several limitations such as the poor design of clinical trials, a reduced number of participants, a lack of common instruments for the neuropsychological evaluation of subjects and the dependence on IQ of individuals that determine prognosis in a given cognitive area.

EGCG is proven to decrease the digestion and absorption of lipids, the secretion of pancreatic lipase and glucose absorption, all of which could lead to a decrease in body weight gain. Xicota et al. (113) studied the influence of EGCG treatment at a 9 mg/kg dosage on body weight in DS adult individuals. Supplementation lasted for 12 months, with a 6 month follow-up after treatment discontinuation. Interestingly, male subjects showed a trend for less body weight gain and lower BMI increase compared to the placebo group, while female participants exhibited no significant effect of EGCG on body composition. Unfortunately, the authors did not provide any data regarding mitochondrial function or energy intake and were unable to explain specific mechanisms related to the observed effect. Further research is needed to confirm and explain the suggestions provided by this particular research.

Long et al. (112) conducted research on 348 caregivers of individuals with DS in order to determine the usage and attitudes of green tea extract (GTE)

and/or EGCG among the DS population. The motive behind performing such research is the fact that published reports of preclinical studies gave both positive and negative results after EGCG and GTE usage, and so the authors wanted to characterize the DS community's perception, knowledge and experience of its usage. The majority of participants (61.2%) had never heard of EGCG and never gave it to a DS child; 20.4% had heard about it, but never gave it to a DS child; 4.9% gave it, but stopped giving it; and 13.5% answered that they were currently giving EGCG to their children. Respondents who currently administer GTE or EGCG observed improvements in cognition, learning, memory, increased energy and speech. Of course, self-reporting is certainly a limitation of this study. Among respondents who decided to quit EGCG supplementation, many decided to do so because of the lack of obvious improvements, or because of adverse reactions in some cases, or because of the fact that child did not like the supplement. Caregivers who had heard about EGCG but decided not to give it to the child listed potential side effects and the lack of evidence for its effectiveness as leading reasons. Another important aspect to be seen from this study is that the dosage ranged from 351 mg/day to 2000 mg/day, and very few caregivers consulted a medical professional. This could be potentially alarming, especially since doses from 150–800 mg/kg have been linked to damage in the liver, kidney, thymus, spleen and pancreas in adults.

Resveratrol is a naturally occurring polyphenol isolated from grapes, red wine, peanuts, berries and other plants and has been widely studied for a multitude of health-promoting effects. As in the case of EGCG, it has low bioavailability, extensive metabolism and rapid urinary elimination (108). Resveratrol is mainly metabolized to form glucuronide and sulfate derivatives and colon microflora can produce dihydroresveratrol. Resveratrol metabolites reach their maximum in plasma approximately 30 minutes after intake (114). All mentioned characteristics are considered as poor pharmacokinetic parameters because it is hard to reach pharmacologically relevant doses for clinical use. It is suggested that the bioavailability can be increased by new delivery systems such as encapsulation in yeast cells or solid dispersion, usage of solid lipid nanoparticles carrier or incorporation of resveratrol in liposomes. This results in an increase in the distribution of resveratrol, especially in the brain tissue of the experimental animals. Some structural analogs of resveratrol (methoxylated or glycosylated compounds) have also been synthesized to obtain better bioavailability results (108).

Dietary supplementation with resveratrol in animal models resulted in the improvement of several mitochondrial functions such as oxygen consumption and the activity of respiratory enzymes. Resveratrol is able to activate one of seven NAD^+-dependent deacetylase enzymes, termed sirtuins (SIRT1), responsible for nutrient availability and energy metabolism associated with mitochondria (115). It also activates intracellular effectors such as AMPK and PGC1α, but exact molecular events by which resveratrol exerts neuroprotective action are yet not known in detail (108). At any rate, it has been suggested as a new drug to be tested as a potential therapeutic tool to promote mitochondrial functions, accelerate neurogenesis and counteract some of the DS clinical features (111). Regarding toxicity of resveratrol, it has been determined that there were no side effects in experimental rats in doses up to 700 mg/kg body weight/day (114). The potential activity of resveratrol metabolites have also been examined recently, and they exhibit different functions that have been previously attributed to free resveratrol. Interestingly, it has been observed that free resveratrol can be partially regenerated from its metabolites (116). Even though it is known that *in vivo* concentrations of resveratrol metabolites can be much higher than free resveratrol (114), to the best of our knowledge, resveratrol metabolites have not been discussed as a therapeutic agent for DS features.

Coenzyme Q10

Coenzyme Q10 (CoQ10) is a naturally occurring quinone synthesized by our organism and also introduced in small quantities through the diet. The isoprenic chain, characterized in humans by 10 subunits, confers lyophilic characteristic to this molecule, allowing its ubiquitous incorporation into lipid environments in the organism (35). CoQ10 is also discussed as a possible therapy for the DS phenotype due to its ability to target mitochondrial dysfunction and

counteract oxidative DNA damage. It exerts a variety of biological functions, such as carrying electrons in the mitochondrial respiratory chain, acting as an antioxidant and functioning as a cofactor for numerous enzymes (117). Tiano and Busciglio (118) reported on research in which DS children were treated with 4 mg/kg/day of CoQ10 or placebo for 6 months. They researched DNA damage in peripheral blood lymphocytes in association with DNA repair enzymes to detect oxidized bases. In the younger age group (5–12 years) CoQ10 inhibited oxidative damage to DNA pyrimidines, and in the age group of 13–17 years, oxidized purines were reduced. Tiano et al. (119) conducted a longer study which included 17 DS patients with ages ranging 5 to 17. Participants received CoQ10 at doses of 4 mg/kg/day for 20 months. Treatment resulted in a significant rise of Co10 in plasma, but it did not affect the overall extent of DNA damage. The study highlighted some age-specific differences in the distribution of the cells according to the integrity of their DNA. Nevertheless, the observed difference was not statistically significant, and it should be considered in relation to the transition to puberty (age group 13–17) associated with estrogen production, and the fact that sex hormones are known to modulate antioxidant-related gene expression. Larsen et al. (120) published the results of a study which involved 4 years of treatment of 32 DS patients with CoQ10 in a form of a ubiquinone (reduced form). They concluded that long-term treatment did not affect DNA or RNA oxidation in children with DS.

Importance of proper dietary habits

When talking about nutritional supplementation, an important question to be asked regards a proper diet and dietary nutrients. Why are the first line of defense against different issues related to DS nutritional supplements instead of a real diet? Kurutas (72) states that there is evidence that people who eat fruits and vegetables have decreased risk for neurological, heart diseases and some types of cancer, but this hypothesis is not confirmed in the case of antioxidant supplements. Interestingly, when comparing the number of published scientific papers related to supplementation and a healthy diet, there is a several-fold higher number of papers in favor of supplements. Although none of the above-mentioned theories has yet proven to be useful in an independent random clinical study on humans, the popularity of different supplements and pressure on parents as well on medical professionals is currently rising. There are several causes which explain this: when talking about the supplements industry, we must not forget that it is a global business worth billions of dollars (12, 71, 121). Besides this, raising a child and/or taking care of an adult with DS causes many feeding issues, so it seems easy and suitable to take a pill. Of course, the general knowledge of caregivers regarding a healthy diet is certainly not adequate to support an increased intake of particular nutrients through food.

The feeding habits and healthy lifestyles of individuals with DS have been studied in many research works. Often, children with special needs have significant feeding skill delays that reflect their developmental level rather than their chronological age. A careful evaluation of the type, textures and quantity of foods consumed is needed to ensure the child is meeting their nutrient and energy needs (122). Feeding problems often start from birth since DS infants have a smaller oral cavity which makes it easier for liquids to spill from the sides of the mouth. Dental abnormalities, which are typical for DS children, result in difficulties with chewing and can contribute to poor nutrition because they are consequently offered soft, high-energy food without the opportunity to accept meats, fresh food and vegetables (123). DS is associated with lowered metabolic rates, resulting in decreased energy needs (122). So, energy intake in both children and adults needs to be calculated to their height and weight and to physical activity, but at the same time, children and adults with DS need the same range of nutrients as the general population. Obesity is common in DS in children and adult population, so it is very important to encourage healthy choices in childhood (123). Vitamin and mineral deficiencies are also observed in DS children (124). B group vitamins are of particular interest since they are responsible for intellectual development and their deficiencies result in intellectual disabilities (125). Cartlidge and Curnock (126) reported a case study of a DS girl who became lethargic and withdrawn as a result of B12

malabsorption and a deficit. Very important is the conclusion that even doctors tend to stereotype DS children with symptoms of mental slowness as part of the syndrome. It is important to consider other causes, as it would be for children without DS. Anecdotal testimonies of improvement in cognitive and intellectual behavior after the usage of nutritional supplementation could be explained by actual improvements in the vitamin and/or mineral statuses of DS individuals. None of the advocate studies in favor of supplement usage have ever explained eating habits with correlation to blood level of specific nutrients in DS participants. Mazurek and Wyka (125) point out that the early onset of Alzheimer's disease in DS is mainly due to genetic factors but also nutritional ones, where diets rich in fats and straight-chain carbohydrates enhance the accumulation of atheromatous plaques and hypercholesterolemia together with vitamin and mineral deficiencies.

Intervention in adequate eating habits in order to improve food and nutrient intakes are proven to have beneficial effects on the overall health of Alzheimer's disease individuals (127). In order to slow down Alzheimer's disease in individuals with DS, parents should take measures for its prevention at the earliest years. This includes a diet rich in vitamins, especially B group, antioxidants (vitamin E), minerals (particularly Mg), dietary fiber and omega-3 fatty acids (125). In any case, standard dietary recommendations for heathier lifestyles (eating more fruit and vegetables and oily fish) may have the added potential benefits of increasing antioxidant intake. Unfortunately, these are often least favoured by individuals with DS (123). Gelb (128) reported that among 240 DS participants, none had a sufficient intake of vitamins and trace elements, especially in the group with a BMI > 75. The author also highlighted the fact that parents, school and society in general do not pay suitable attention to the diet and physical activity of DS children. In this sense, parents have especially important role since they are shaping eating habits as role models (129). The physical activity of DS children is another problem connected to hypotonia and very relaxed ligaments. Therefore, some activities should be avoided to prevent injuries. Still, there are numerus possibilities for physical activity, and children should be encouraged to increase their function, improve fitness, expand energy for weight management and have fun (130). In the end, when both exercise and nutrition interventions are combined with a more comprehensive health behavior education program, stronger evidence exists for reductions in weight. This leads to better fitness and health and an improved quality of life. Such interventions can also potentially reduce health care costs through the prevention of secondary conditions (131). An interdisciplinary team which includes parent/caregivers, a nutritionist, physician and medical professionals should be included in the determination of appropriate feeding methods, type and textures of foods, and of course the quantity of food in order to achieve best results for improvement of nutritional status of DS children and adults (122).

Conclusions

Although there is a large amount of promising research which implies the possible benefits of some supplements on the health status, intellectual and cognitive development of individuals with DS, to date, they have not been proved by independent scientific studies. The confirmation of such theories and development of therapies which are undoubtedly effective and safe is a challenge for scientists which is yet to be answered. In the meantime, parents and caregivers of individuals with DS should consult medical and nutritional professionals prior to the introduction of such therapies. DS patients (as all others) should primarily obtain their necessary nutrients from a diet. To do so, caregivers and parents should be included in educational programs regarding a healthy diet and lifestyle, with support of health and social care professionals, different DS associations, and—above all—scientists.

Abbreviations

DS: Down syndrome; Ts21: trisomy of chromosome 21; Hsa21: human chromosome 21 genes; FDA: food and drug administration; HAP caps: high achievement potential capsules; Zn: zinc; Cu: copper; Mn: manganese; Se: selenium; TNI: targeted nutritional intervention; RDA: recommended

daily allowance; ROS: reactive oxygen species; $O_2^{\bullet-}$: free radical superoxide; $OH^{\bullet}$: hydroxyl radical; H_2O_2: hydrogen peroxide; SOD: superoxide dismutase; GPx: glutathione peroxidase; CAT: catalase; DSCR: Down syndrom critical region; Ts65Dn: Down syndrome mouse models; Ts1Cje: Down syndrome mouse models; SOD1: superoxide dismutase 1; ATP: adenosine triphosphate; OXPHOS: oxidative phosphorylation; APP: amyloid-β precursor protein; EGCG: epigallocatechin gallate; SOD2: superoxide dismutase 2; RCAN1: regulator of calcineurin 1; TBARS: thiobarbituric acid reactive substances; MDA: malondialdehyde; 8-OHdG: 8-hydroxy-2-deoxyguanosine; ZnT: zinc transporters; AMPK: activated protein kinase; PGC-1α: peroxisome proliferator-activated receptor-y coactivator 1α; GTE: green tea extract; SIRT1: termed sirtuins; CoQ10: Coenzyme Q10; MSN: medial septal nucleus; BFCNs: basal forebrain cholinergic neurons; NGF: nerve growth factor; TIBC: total iron-binding capacity; GR: glutathione reductase; GGT: gamma-glutamyl transferase; G6PD: glucose-6-phosphate dehydrogenase; MPO: myeloperoxidase; GSH: reduced glutathione; GSSG: oxidized glutathione; UA: uric acid; GST: glutathione transferase; PC: protein carbonyls; AGE: advanced glycation end products; diTyr: dityrosine; NO_x: nitrite/nitrate.

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