Review Article

Indian J Med Res 142, August 2015, pp 113-119
DOI:10.4103/0971-5916.164218

Oxidative stress, thyroid dysfunction & Down syndrome

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Received April 17, 2014

Down syndrome (DS) is one of the most common chromosomal disorders, occurring in one out of 700-1000 live births, and the most common cause of mental retardation. Thyroid dysfunction is the most typical endocrine abnormality in patients with DS. It is well known that thyroid dysfunction is highly prevalent in children and adults with DS and that both hypothyroidism and hyperthyroidism are more common in patients with DS than in the general population. Increasing evidence has shown that DS individuals are under unusual increased oxidative stress, which may be involved in the higher prevalence and severity of a number of pathologies associated with the syndrome, as well as the accelerated ageing observed in these individuals. The gene for Cu/Zn superoxide dismutase (SOD1) is coded on chromosome 21 and it is overexpressed (~50%) resulting in an increase of reactive oxygen species (ROS) due to overproduction of hydrogen peroxide (H_2O_2). ROS leads to oxidative damage of DNA, proteins and lipids, therefore, oxidative stress may play an important role in the pathogenesis of DS.

Key words Down syndrome - oxidative stress - reactive oxygen species - thyroid dysfunction

Down syndrome (DS) or trisomy 21 is one of the most important human congenital diseases. The syndrome is associated with mental retardation, congenital heart disease, immune system disorders, digestive problems, endocrine system deficits and different biochemical disorders. It could be speculated that the chromosome abnormality led to impaired formation of the thyroid and other organs[1]. The association of DS with thyroid disorders has been known for decades. Thyroid dysfunction is highly prevalent in DS[2-5]. Patients with DS have an increased prevalence of autoimmune disorders affecting both endocrine and non-endocrine organs[3]. Thyroid disorders have been reported to have a prevalence rate of 3-54 per cent in individuals with DS and these increase in frequency with increasing age of the individual[3]. Another risk factor is the female sex[6]. It has been suggested that individuals with DS are under unusual oxidative stress, which has been proposed to be caused by an excess of Cu/Zn superoxide dismutase (SOD1) activity, an enzyme coded on HSA21 (21q22.1)[7-11]. SOD1 enhances the production of hydrogen peroxide (H_2O_2), an important precursor of hydroxyl radical, being one of the at least 16 genes or predicted genes on HSA21 with a role in mitochondrial energy generation and reactive oxygen species (ROS) metabolism[10]. H_2O_2 is then neutralized to water and oxygen through the actions of either glutathione peroxidase (GPx) and/or catalase (CAT). Hence, the increased ratio of SOD1 to catalase plus

glutathione peroxidase can lead to increased oxidative stress in DS[12]. The aim of this article was to critically review the scientific literature concerning the link between oxidative stress and thyroid dysfunction in Down syndrome.

Down syndrome

DS or trisomy 21 is known to occur in one out of 700-1000 live births[13]. Clinical symptoms were first described by John Langdon Down in 1866[14], but the association with one extra copy of chromosome 21 was first reported by Lejeune *et al*[15]. Trisomy 21 is now accepted to be the major cause of DS, accounting about 90-95 per cent of cases. The other 5-10 per cent are caused by other genetic abnormalities including chromosomal translocations (2 to 6%) and mosaicism (2 to 4%)[13,16].

DS patients present different morphological characteristics such as short height, obesity and bilateral epicanthic eyefolds. Furthermore, muscular hypotonia may be noted during life[17]. The syndrome is associated with mental retardation, congenital heart disease, immune system disorders, digestive problems, endocrine system deficits and different biochemical disorders[18,19]. The clinical manifestations of hypothyroidism are so non-specific that it may be attributed to the DS itself. Thyroid hormones are necessary with respect to brain development, and therefore, thyroid disorders should be detected immediately[20]. Besides, DS patients have an increased risk of leukaemia and Alzheimer's disease[21-24].

The extra copy of chromosome 21 (HSA21) or part of it, affecting more than 300 genes, is associated with a variety of manifestations, including pathologies which are possibly related to ageing such as Alzheimer's disease, visual impairment, senile cataracts, leukaemia, diabetes mellitus, hypogonadism, vascular disease, amyloidosis and premature graying or loss of hair, and skin changes[25-27]. Besides, there is evidence of accelerated ageing in individuals with DS, this disorder being considered as a progeroid syndrome[28], and it has been postulated that it may be the result of an increased oxidative stress. The prevalence of clinical disorders in individuals with DS is higher than in the general population, and has a negative impact on their quality of life and life expectancy[29-31].

There is well-established evidence from *in vivo*, *in vitro* studies and animal models that oxidative stress is involved in DS. Thus, it has been proposed that the increased oxidative stress observed in these subjects is mainly caused to an excessive activity of SOD1, an enzyme coded on HSA21 (21q22.1)[32]. Besides, several abnormalities in mitochondrial function have been found in DS and also in mouse models of this pathology[33,34]. In addition to SOD1, there are several genes or predicted genes on HSA21 with a role in mitochondrial energy generation and ROS metabolism[35,36].

Oxidative stress

A free radical is any species capable of independent existence, containing one or more unpaired electrons[37], the most important ones being those derived from either oxygen and/or nitrogen. Both the radicals and the non-radical species generated via interaction with free radicals, are referred to as reactive oxygen/nitrogen species (RONS)[38]. RONS, formed in the human body in the cytosol, mitochondria, lysosomes, peroxisomes and plasma membranes under both physiological and pathological conditions[39], are highly reactive and extremely short-lived agents mainly generated as by-products of aerobic metabolism, playing a dual role as both deleterious and beneficial species. When the generation of RONS exceeds the ability of antioxidant defence systems to remove them, an imbalance between RONS formation and antioxidant defence can cause oxidative/nitrosative damage to cellular constituents (DNA, proteins, lipids and sugars), which is defined as oxidative/nitrosative stress[10,40]. Thus, the degree of balance between ROS or reactive nitrogen species (RNS) determines the degree of oxidative or nitrosative stress, respectively. When the system becomes unbalanced (free radicals > antioxidant defences) a change in the intracellular redox balance towards a more oxidizing environment, may result in direct DNA damage (DNA mutations), changes in the structure and function of proteins, and peroxidative damage to cell membrane lipids with the possibility to cause illness and disease. Though an excess leads to oxidative/nitrosative stress, RONS are also involved in several important biological processes, including cell signalling, redox regulation of gene transcription, cellular immunity and apoptosis, being essential for normal physiological function[41].

Oxidative stress is a process induced by endogenous as well as exogenous factors. Endogenous factors include normal physiological processes, such as oxidative phosphorylation or cytochrome P450 metabolism. Several environmental factors, including smoking, diet or exposure to ambient air pollution, represent exogenous sources of RONS[42]. Increasing

evidence suggests that oxidative stress is linked to the primary or secondary pathophysiologic mechanisms of multiple human diseases, including DS[43,44].

The biological effects of these highly reactive compounds are controlled *in vivo* by a wide spectrum of antioxidative defence mechanisms such as vitamins E and C, carotenoids, metabolites such as uric acid or glutathione and antioxidant enzymes. Cells have developed an enzymatic antioxidant pathway against free radicals and ROS which are generated during oxidative metabolism: firstly, SOD1 catalyzes the formation of hydrogen peroxide from superoxide radicals[45]. An excess of the enzyme SOD1 activity has been considered to be responsible for the increased oxidative stress found in this condition. The gene encoding SOD1 is located on HSA21, so DS individuals are trisomic for SOD1. SOD1 is overexpressed in about 50 per cent of these individuals[9,46]. This enzyme plays a key role in the metabolism of ROS, being part of the first line of antioxidant defence by catalyzing the dismutation of superoxide radical (O_2^-), mainly generated by oxidative metabolism, into oxygen plus H_2O_2[47]. SOD1 is the major cytoplasmic superoxide scavenger, also located in the intermembrane space of the mitochondria[48].

Hydrogen peroxide can generate toxic hydroxyl radicals, but it is removed by a reaction catalyzed by CAT and GPx[49]. Glutathione reductase (GR) is a flavoprotein catalyzing the NADPH-dependent reduction of glutathione disulphide (GSSG) to glutathione (GSH), which is essential for the maintenance of glutathione levels. Any increase in SOD catalytic activity produces an excess of hydrogen peroxide that must be efficiently neutralized by CAT or GPx. The activity of the first and second step antioxidant enzymes must, therefore, be balanced to prevent oxidative damage in cells, which may contribute to various pathological processes[50].

The trace element selenium (Se) is capable of exerting multiple actions on endocrine systems by modifying the expression of at least 30 selenoproteins, many of which have clearly defined functions. Well-characterized selenoenzymes are the families of glutathione peroxidases (GPx), thioredoxin reductases (TRs) and iodothyronine deiodinases (Ds). These selenoenzymes are capable of modifying cell function by acting as antioxidants and modifying redox status and thyroid hormone metabolism[51]. Se is also involved in cell growth, apoptosis and modifying the action of cell signaling systems and transcription factors. During thyroid hormone synthesis GPx1, GPx3 and TR1 are upregulated, providing the thyrocytes with considerable protection from peroxidative damage[51].

The thyroid contains more Se per gram of tissue than any other organ[52] and Se, like iodine, is essential for normal thyroid function and thyroid hormone homeostasis. Synthesis of thyroid hormone requires iodination of tyrosyl residues on thyroglobulin which is stored in the lumen of the thyroid follicle. This iodination is catalyzed by thyroid peroxidase (TPO) and requires the generation of high H_2O_2 concentrations which are potentially harmful to the thyrocyte[51].

The thyrocyte is continually exposed to potentially toxic concentrations of H_2O_2 and lipid hydroperoxides. The cytotoxic effects of H_2O_2 on thyroid cells include caspase-3-dependent apoptosis that occurs at H_2O_2 concentrations that are insufficient to induce necrosis. In Se deficiency the apoptotic response to H_2O_2 is increased[53]. When Se intake is adequate, the intracellular GPx and TR systems protect the thyrocyte from these peroxides.

Oxidative damage can be monitored by the determination of different oxidative stress biomarkers. Several studies have shown higher levels of protein carbonyls, malondialdehyde, allantoin or 8-hydroxydeoxyguanosine in DS than in normal population[54-57].

Thyroid dysfunction

Thyroid hormones (THs) are associated with oxidative stress and antioxidant status due to their capacity to accelerate the basal metabolism and change respiratory rate in mitochondria[58]. However, THs are related to oxidative stress not only by their stimulation of metabolism but also by their effects on antioxidant mechanisms[58]. These regulate proteins, vitamins and antioxidant enzymes synthesis and degradation[59] as well as oxygen consumption and mitochondria energy metabolism, playing an important role in free radical production[59]. It has been suggested that variations of thyroid hormones levels can be one of the main physiological modulators of *in vivo* cellular oxidative stress[60]. Thyroid dysfunction is the most frequent endocrine abnormality in subjects with DS, with a prevalence varying between 0 and 66 per cent, depending on variations in population size, age, laboratory assays or definitions of thyroid dysfunction used, the more common rates being >20 per cent[61]. Hypothyroidism is the most frequent thyroid abnormality in DS[2,62]. It can be either congenital, with an incidence in infants with DS of 1:141 live births[2]

compared with an incidence ranging between 1:2,500 and <1:5,000 among newborns without DS[63], or acquired at any age after birth. Claret *et al*[29] have observed that the hypothyroidism characteristic of early infancy in DS usually presents as a subclinical disorder. The distribution of the disorder in this initial stage is similar between sexes, which contrasts with that found in the population without DS, where the hypothyroidism is clearly predominant in the female sex[3]. However, more evidence is required regarding the optimal course of treatment for subclinical hypothyroidism[64]. Hyperthyroidism is also more prevalent among people with DS than in the general population, though the gap is smaller[62,65].

The available data concerning oxidative stress in both hypothyroidism and hyperthyroidism are scarce and controversial. In hypothyroidism, a low free radical generation is expected because of the metabolic suppression brought about by the decrease in thyroid hormone levels[66]. However, there are some studies reporting an increased oxidative stress in patients with hyperthyroidism as well as with hypothyroidism[57,67-70], even in subclinical hypothyroid states. In addition, thyroid hormone (T_3) has been shown to downregulate the expression of SOD1 and, conversely, progressive hypothyroidism leads to an increase in SOD1 activity in the brain of rats[71].

Only a few investigations have been conducted addressing the link between thyroid dysfunction and oxidative stress in DS, all of these in hypothyroid subjects. Kanavin *et al*[72] were the first studying the link between oxidative stress and thyroid dysfunction in DS, suggesting that hypothyroidism is linked to decreased levels of selenium in DS subjects. Oxidative and nitrosative stress have been assessed in hypothyroid DS subjects receiving levothyroxine for treatment of hypothyroidism by measuring a set of urinary biomarkers: 8-hydroxy-2'-deoxyguanosine (8-OHdG), isoprostane 15-F2t-IsoP, thiobarbituric acid-reacting substances (TBARS), advanced glycation end-products (AGEs), dityrosine (diTyr), hydrogen peroxide and total nitrite and nitrate (NOx), in children[73] and in adolescents and adults[74]. In these studies, significantly higher levels of diTyr in children with DS receiving levothyroxine for hypothyroidism have been found compared to their healthy siblings. Besides, subjects with DS receiving levothyroxine showed increased levels of diTyr in the early adulthood (from 15 to 19 yr) and increased levels of diTyr, AGEs and TBARS in the adulthood (from 20 to 40 yr) than in those without hypothyroidism. Both hypothyroid and hyperthyroid patients are characterized by higher levels of low density lipoprotein (LDL) oxidation when compared with healthy normolipidemic control subjects[67], which may explain the increased levels of urinary TBARS. In hyperthyroid patients increased lipid peroxidation was strictly related to free thyroxine levels, while in hypothyroidism it was strongly influenced by serum lipids[67]. Therefore, lipid composition must be studied in hypothyroid DS subjects before any conclusion can be reached.

Decreased urinary levels of creatinine (Cr) were observed in DS children receiving levothyroxine compared to their non-DS healthy siblings[73,75]. Besides, lower levels of urinary Cr have been found in the early adulthood (from 15 to 19 yr) of DS subjects receiving levothyroxine compared with DS subject without diagnosed hypothyroidism[75]. Hence, renal impairment due to hypothyroidism may bias the results in these patients as has been suggested by the authors[75]. It is well known that levels of Cr are influenced by thyroid hormones. Hypothyroidism enhances serum Cr levels because it reduces the glomerular filtration rate and increases production of Cr[76]. Impaired renal function has been reported in subjects with hypothyroidism[77]. It has also been reported that non-DS children with congenital hypothyroidism have an increased prevalence of congenital renal and urologic anomalies[78], and renal impairment has also been described in DS based on decreased Cr clearance[79,80].

Reduced Cr clearance in non-DS patients with hypothyroidism had been reported, but normal values were obtained when they were treated with thyroid hormones[77]. However, the same has not been found in DS[76,78], suggesting that factors contributing to the aetiology of hypothyroidism may be different in DS than in non-DS individuals.

Some abnormalities reported in DS may influence the thyroid function: *(i)* decreased levels of selenium[81], which is required for thyroid hormone synthesis and metabolism, acts as an antioxidant protecting the thyrocyte against peroxides and is part of selenium-dependent antioxidant enzymes (*e.g.* GPx and thioredoxin reductase), *(ii)* an impairment in the activity of phenylalanine hydroxylase[82], which converts the phenylalanine in tyrosine, and *(iii)* overexpression of DYRK1A kinase[83], which could reduce availability of tyrosine. These factors may lead to several anomalies related to thyroid disorders, even in DS subjects with "normal" thyroid hormones levels. However, further investigation is required to ascertain the mechanisms underlying these findings. On the other hand, signs

and symptoms of hypothyroidism can be difficult to discriminate from those found in the natural course of DS itself. These are overlapped to some extent in both DS and hypothyroidism (*e.g*. hypotonia, lethargy, mental retardation, growth failure, prolonged neonatal jaundice, delayed closure of fontanelles, macroglossia, obesity, *etc*.)[84]. Although it has been reported that mild plasma thyroid stimulating hormone (TSH) elevation is prevalent in DS: 80-90 per cent in early infancy and 30-50 per cent thereafter[85], untreated subclinical hypothyroidism is present in DS at birth and persists throughout life[86]. In summary, more studies linking thyroid disorders and oxidative stress in DS are clearly needed.

Conclusions

Thyroid dysfunction is the most frequent endocrine abnormality in patients with DS. There are studies reporting an increased oxidative stress in patients with hyperthyroidism as well as with hypothyroidism, even in subclinical hypothyroid state. In addition, thyroid hormone (T_3) has been shown to downregulate the expression of SOD1. Some abnormalities reported in DS may influence the thyroid function: *viz*. decreased levels of selenium, impairment in the activity of phenylalanine hydroxylase, and overexpression of DYRK1A kinase. However, many aspects that are crucial for the health and well-being of people with this condition remain to be elucidated and require further research.

Acknowledgment

The authors thank María Burgos for English correction of the manuscript, and Nieves Fonturbel for her help with bibliographic compilation.This study was supported in part by Fundación Inocente, Inocente, Madrid, Spain.

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