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Down syndrome and thyroid dysfunction: Should nutritional support be the first-line treatment?

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Summary Individuals with Down syndrome (DS) not only have increased risk of hypothyroidism, they also tend to develop a relatively novel mild form of neonatal hypothyroidism. One problem that may predispose those with trisomy 21 to hypothyroidism is the overexpression of the gene DYRK1A, which may have an affect on the thyroid. While thyroxine supplementation (such as Synthroid) is increasingly being advised for those with DS, this treatment may have both positive and negative effects. Nutritional support for hypothyroidism offers some of the same benefits as drug therapy but without the likely negative long-term effects. Early 20th century practitioners used bovine glandulars for those with DS children, which were believed to help support thyroid function. Some doctors in more recent times have also included iodine, L-tyrosine, selenium, and zinc. As nutrition for those with DS has been safely used by some practitioners for many decades, it is suggested that nutritional thyroid support, and not necessarily thyroxine, should be considered for use as a first line treatment for those with trisomy 21. This paper also hypothesizes that nutritional interventions begun prenatally by the mother, may possibly also be of benefit.

Introduction

People with Down syndrome (DS) are much more likely to have or develop hypothyroidism than the general public [1]. Furthermore, it appears that even neonatates with DS tend to be mildly hypothyroid [2].

In DS (also known as trisomy 21), there is an extra copy of the 21st chromosome. Many enzymes that are encoded on the extra 21st chromosome are known to be actively transcribed, which results in overexpression of these enzymes. It has been speculated that there is a direct relationship with the overexpression of the twenty-first chromosome and the development of hypothyroidism, perhaps, through genetic interference with thyroid hormone production [2] or through oxidative stress [3], which is increased in those with DS.

Because of the high occurrence of even mild hypothyroidism, some have advocated thyroxine therapy for those with DS (e.g. [2,4]).

One clinical manifestation of trisomy 21 is that both males and females with DS tend to be much shorter than the non-DS population, even into adulthood [5]. Interestingly, van Trotsenburg

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et al. have reported that thyroxine (T-4) therapy begun for neonates appears to improve the growth and development for those with DS [6].

While there appears to be benefits associated with thyroxine therapy for those with DS, there are also a few risks. Since the hormone TSH (thyroid stimulating hormone, also called thyrotropin) is released when lower levels of T-4 are in the blood, the taking of thyroxine artificially elevates serum T-4 levels and hence reduces the anterior pituitary gland's production of TSH. Actually one of the claimed benefits of taking synthetic thyroxine is that it ''is also effective in the suppression of pituitary TSH secretion...'' [7], but this ''benefit'' comes with a cost.

Ultimately, the reduction of TSH means that the thyroid is getting less stimulation to make any of its hormones, including calcitonin (also referred to as thyrocalcitonin), monoiodotyrosine (T-1), and diiodotyrosine (T-2). Triiodothyronine (T-3) is less of a factor as certain tissues, (especially the liver) converts T-4 back into T-3 (T-4 can also convert into rT-3, which is believed to be inactive). In addition to T-4 and T-3, the thyroid also secretes small amounts of calcitonin and thyroglobin into the blood — thyroglobin contains T-1, T-2, T-3, and T-4 [8,9]. The hypothalamus is also be involved with the thyroid as it secretes the thyrotropin-releasing hormone in response to both TSH and T-4 [9].

The hormone calcitonin helps prevent calcium losses from the bones [1] and long-term use of thyroxine-containing medications has been suspected in increasing the frequency of osteoporosis by some researchers (i.e. [10—12]), but the results are considered to be inconclusive for men. (Vitamin D variations are also suspect in that hypothyrioid/hypometabolic people have an aerobic deficit that counteracts D-disorders of vitamin D metabolic have been suspected in DS.)

Although T-1 and T-2 are often considered to be of no metabolic use on their own, some doctors have long believed that supporting the production of them nutritionally can improve weakened brain activity, fatigue, and depression [13] and even assist in weight control. In addition, recent research is concluding that T-1 and T-2 actually do have biological importance [14].

Thyroxine therapy is relatively safe (though if it converts to rT-3, it can be ineffective). Yet, it is accepted that thyroxine therapy can decrease bone density for women and increase the risk of occult cardiac disease in older patients with cardiovascular disease (nearly 1/2 of those with DS have some type of cardiac disorder) [7]. ''Generally, replacement therapy is to be taken for life'' [7], because thyroxine therapy can contribute to thyroid atrophy through interfering with TSH production.

The most common form of thyroid replacement medicine is Synthroid. Synthroid is composed of synthetic crystalline tetraiodothyronine (thyroxine, T-4), plus the herb acacia, confectioner's sugar (with corn starch), lactose monohydrate, talc, various artificial colors, and other presumed inert substances [7]. Recognized side effects of thyroxine therapy can include fatigue, increased appetite, weight loss, heat intolerance, excessive sweating, headache, nervousness, anxiety, irritability, insomnia, tremors, muscle weakness, heart failure, angina, myocardial infarction, dyspnea, diarrhea, vomiting, abdominal cramps, hair loss, decreased bone mineral density, menstrual irregularities, and fever [7].

The prescribing of thyroxine-containing medication is intended to directly replace or supplement the body's production of T-4 [7] and indirectly support the levels of T-3. Thus the prescribing of thyroxine normally (unless the intention is thyroid-suppression) presupposes that the body is somehow incapable of producing sufficient quantities of T-4 and T-3 on its own.

But is that presupposition true?

While thyroid support may be beneficial for nearly every person with DS, it is not clear that thyroxine-containing medications are always the best option available.

What if the problem is simply one of a deficiency of key nutrients and/or enzymes needed by the thyroid?

If so, might nutrition be something to consider?

Nutrition as an intervention strategy

The idea of using nutrition to support the thyroid is not a new one. Actually, the Chinese have been using kelp (a high iodine-containing food) as a specific treatment for hypothyroidism, for thousands of years [15].

The physiological basis of the use of nutrition for the thyroid is relatively clear as its hormones involve certain key nutrients. T-1 is called monoiodotyrosine (or simply iodotyrosine). T-1 is composed of iodine and tyrosine that normally come together after the iodine has been associated with an iodinase enzyme [8]. After it undergoes metabolic processes, which involve more iodine it becomes T-2, and then some type of coupling occurs to form T-3 and T-4 [8,9]. The later conversion of T-4 into T-3 requires a selenium-containing enzyme. Zinc is also involved. The conversion of T-4 into reverse T-3 (rT-3) also utilizes selenium.

Selected thyroid nutrients

Iodine

Many foods contain iodine (such as sea vegetables). Recent research has confirmed that seaweed sources do provide bioavailable iodine [16], and that seaweeds are probably the primary source of iodine in countries such as Japan [9]. The thyroid must trap about 60 mcg of iodine each day to maintain an adequate amount of thyroxine and at least one billion people living in developing countries are currently believed to be deficient in iodine [17]. The daily RDA for iodine is 150 mcg for adults, 90 mcg for children 1—8, 120 mcg for children from 9—13 [9] and ''the thyroid is the only organ known to organify iodine'' [18].

Iodine is the densest of the common halogens [9]. In one study, van Trotsenburg et al. concluded that iodine exposure preceding their neonatal screening was not a cause of mild hypothyroidism in DS neonatates [19]. Yet, it needs to be understood that iodine is the easiest of the halides to oxidize, and over-expression of superoxide dismutase (SOD-1) results in decreased superoxide anion (the enzyme substrate) and increased hydrogen peroxide (the enzyme byproduct). Hence, for those with DS, it is likely that more than iodine exposure needs to be considered. In addition, higher-than-normal demands on selenium reserves caused by glutathione-peroxidase induction may compromise selenium-containing deiodination enzymes that are responsible for peripheral conversion of T-4 into either T-3 or reverse T-3, either of which might be involved in mild hypothyroidism.

L-Tyrosine

L-Tyrosine is essential for certain thyroid and adrenal hormones [8]. It is considered to be a non-essential amino acid, which means that if everything is working correctly in the body (which is not always the case with DS), it can convert phenylalanine into tyrosine. However, since it has a synthesis component limited by phenylalanine oxidation, there appears to be more problems producing sufficient quantities of L-tyrosine than other non-essential amino acids [20,21]. And this is more of a problem in those with DS, probably because the activity of phenylalanine hydroxylase is impaired in the liver of those with DS [20].

There are apparently also other tyrosine issues for those with DS. Even in utero those with DS have a 50% overexpression of the kinase DYRK1A (DYRK1A is an abbreviation for dual-specificity tyrosine (Y) regulated kinase 1A), which is partially regulated by tyrosine [22] — it may be that this overexpression of DYRK1A further reduces the available tyrosine for those with DS. DYRK1A is considered to be a candidate for causing the mental retardation and some of the other negative side effects associated with DS [23,24]. It is possible that consumption of supplemental tyrosine or certain peptides might result in reduced DYRK1A levels (as one such peptide has been successfully tested, [24]), and hence be of benefit to the DS population—but this needs more study.

Selenium

DS patients may have below-normal plasma levels of selenium [3,25,26]. This may be a direct consequence of increased incorporation of selenium into glutathione peroxidase, which is induced to higher-than-normal levels by excessive SOD-mediated hydrogen peroxide production. Selenium may be beneficial in DS by protecting the biosynthesis of thyroxine from free radical attack [3]. Because of its demonstrated abilities to reduce oxidative stress, high selenium yeast may be the preferred form for those with DS [27,28].

''The iodothyronine deiodinases, types I—III are all selenoproteins. These enzymes catalyze the deiodination of thyroxine. . .{into} triiodothyronine, and reverse triiodothyronine and thereby regulate the concentration of the active hormone triiodothyronine'' [29]. Kanavin et al. have suggested that it is the oxidative stress present with DS that reduces available selenium levels and thus is a major contributor to hypothyroidism in the DS population [3]. Since selenium is essential for the production of proper thyroid hormone levels, supplementation with it may be doubly helpful for those with DS.

Zinc

Reports suggest that DS patients have below-normal plasma levels of zinc [30,31]. Zinc is often recommended to assist with oxidative stress [32]. ''Circulating triiodothyronine and thyroxine are decreased in zinc deficiency, as is the hypothalamic thyroid-releasing hormone'' [33]. One found that zinc reduced TSH by 34% for hypothyroid Down syndrome patients [34], Zinc deficiency may thus account for some of the hypothyroidism in DS.

Other substances: glandulars

While the late Turkel is often considered to have pioneered the use of nutrition for those with DS, the fact is that doctors who used glandular nutrition preceded his work by decades. Early practitioners specifically used glandulars for children with DS to help support thyroid function (including TSH production) as well as to improve overall development [35].

Some doctors in more recent times, like the late Jack Warner (who claimed to have been Turkel's selected successor for following his approach for using nutrition for those with DS) have included glandulars in their nutritional approaches for those with DS. It may be of interest to note that Warner, like van Trotsenberg, claimed that his approach (which was primarily nutritional) improved delayed development associated with DS [36]. An independent study by one of this paper's authors found that Warner's protocol did improve the height of children with DS [37]. Whether this was due to the glandulars and/or the thyroid-supporting nutrients in Warner's protocol such as iodine, L-tyrosine, selenium, and zinc was not clear. But it is interesting to note that both Warner's nutritionally-based intervention [37] and van Trotsenburg's thyroxine-based intervention [6] did result in statistically significant improvements in height for those with DS.

Regarding glandulars, evidence suggests that with oral consumption of glandular extracts, a small percentage (5–10%) of their peptides are not broken down into their constituent amino acids but are available for intact absorption in the small intestine [38–41]. A small amount of these absorbed peptides then circulate and some of them appear to assist the human body (especially for ill persons) in performing various anabolic and catabolic processes [38–42]. Howell and others have reported that the amount of enzymes that pass through the stomach is between 40% and 50% [43].

Although the use of glandulars has its critics [4,18,44], a study in the *Journal of Surgery* showed that oral pancreatic supplementation resulted in improved enzyme and growth levels for children who had a pancreaticoduodenectomy [45]. Oral consumption of a bovine thymus extract has been shown to reduce the frequency of recurrent respiratory infections and increase salivary IgA in children [46]. Other glandular substances are used regularly by the medical community. Additionally, papers have suggested that bovine glandulars may be helpful for thyroid support [47], myoclonic seizures [47], anti-inflammatory activities [18], and immune response [18,48].

It has been specifically claimed that glandulars may work by having a protective ability against autoimmune reactions against the related organs, ''Glandulars, said Lee, neutralize such attacks'' [49,50]. Autoimmune reactions are believed to be the major cause of primary hypothyroidism in the non-DS population [1].

It should be noted that many substances contained within animal tissues are similar or identical to their human counterparts [51–54], including certain enzymes [52], hormone biological activities [54], necessary trace minerals [50,55], and even T-cell gene regions [53], though commercially available bovine thyroid (as often used by one of the authors, 47) does not contain detectable amounts of T-4 [18]. This is helpful since the highly prescribed porcine thyroid medication does contain T-4 and, similarly to thyroxine, can artificially cause lowered TSH. Perhaps, it should be noted that no negative long-term side effects are known to occur with bovine (cow) or ovine (sheep) glandular extracts [56]. Note: research performed a century ago concluded that because of immune response and other factors, extracts from ruminants (cows/sheep) were often preferable over other sources for humans [50,57].

The reason that the best most commercially available bovine thyroid tissue is low-temperature dried is so it will contain its natural thyroid enzymes [49]. These thyroid enzymes would be expected to play a role in the organification of iodine, the utilization of tyrosine, and the production of all the known thyroid hormones. Few metabolic processes occur in the human body without specific enzymes [43]. It may be that thyroid glandulars contain substances that may help normalize DYRK1a levels, but this needs much further investigation.

While it is true that the world would benefit from further elucidation on precisely all the reasons why glandulars work, the simple fact is that certain clinical practitioners long claimed to have successfully used glandulars for many decades for those with DS and other health concerns.

Discussion

In one of the author's clinical experience, unless a thyroid has been surgically-removed and/or ablated, thyroid glands are capable of producing T-4 on their own if properly supported nutritionally. And this has been true whether or not patients have DS.

Thyroxine therapy often does result in a reduced production of calcitonin, T-1, and T-2. Is this something that should become standard therapy for DS infants when other alternatives exist?

Since, there are issues related to the lack of available tyrosine and/or available iodine in DS, it is likely that nutrition contributes to the wide prevalence of hypothyroidism in the DS population. This also may be compounded by low selenium and zinc levels, which have been noted for this population. Because these factors are known, it may make sense for pregnant women to supplement with thyroid-related nutrients in an effort to possibly

reduce the mild hypothyroidism that most with DS seem to be born with.

While it is true that prescribed thyroxine levels are normally monitored with TSH to try to keep TSH in a predetermined range [1] (and this is only true when neuroendocrine feedback systems are normal, which is highly arguable), it is not clear that this is still optimal for health, especially the health of those with DS.

While some may conclude that there are too many nutritional factors to be considered and that thyroxine medication is an easier fix, the reality is that the long-term consequences of artificially suppressing thyroid function through thyroxine therapy poses greater potential future complications. Should any human be required to live their entire life with externally affected TSH levels when it may not be necessary?

And if not, then nutrition does offer the logical alternative for those with DS. (It perhaps should be noted that many of the comments in this paper are also applicable to those hypothyroid patients without DS.)

It perhaps should be noted that the efficacy of multi-nutrients in DS alone, though advocated by some (i.e. [28,58,59]), has been discounted by others (i.e. [60–62])—but none have apparently focused on the possible efficacy of certain nutrients related to the thyroid in this population. Although it has been claimed regarding hypothyroidism that, ''supplemental thyroid products are not useful for this purpose'' [18], this is not consistent with the clinical experience of various practitioners [13,35,36,39–41,49,50,56] nor one of the authors. One of this paper's authors found that using bovine thyroid glandulars and/or other nutrients for the thyroid reported in symptomatic improvement for 217 of 220 non-DS patients presenting symptoms associated with hypothyroidism [63] and that bovine thyroid glandulars have also been helpful for those with DS [47].

Irrespective of these controversies, a review of the nutrients, enzymes, and other substances associated with the thyroid suggests that it is logical that certain nutrients, which are helpful for the thyroid may also be preventive for some of the negative metabolic processes involved in DS. Nutrition for hypothyroidism is something that is frequently missed by doctors in clinical practice as medications are most often emphasized (e.g. [64]).

Considering the relative safety and theoretical benefits of the above-mentioned nutrients, as well as the inevitability of thyroid issues in the untreated DS population, it seems wise to seriously consider such supplementation. It seems equally wise to undertake additional research long-term research to verify the safety and efficacy in providing DS neonatals thyroxine therapy for an entire lifetime, beginning at birth. This is not to say that the risks of thyroxine therapy for the DS population always exceed the benefits, only that nutrition seems to be a wiser, and more universally appropriate, thyroid therapy for those with DS.

Since, reasonable levels of nutrient supplementation directed towards the thyroid is safe and without likely long-term negative consequences, it makes sense to consider thyroid nutrition as the first-line treatment for those with DS.

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