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Central hypothyroidism — a neglected thyroid disorder

Paolo Beck-Peccoz[1], Giulia Rodari[2], Claudia Giavoli[2] and Andrea Lania[3]

Abstract | Central hypothyroidism is a rare and heterogeneous disorder that is characterized by a defect in thyroid hormone secretion in an otherwise normal thyroid gland due to insufficient stimulation by TSH. The disease results from the abnormal function of the pituitary gland, the hypothalamus, or both. Moreover, central hypothyroidism can be isolated or combined with other pituitary hormone deficiencies, which are mostly acquired and are rarely congenital. The clinical manifestations of central hypothyroidism are usually milder than those observed in primary hypothyroidism. Obtaining a positive diagnosis for central hypothyroidism can be difficult from both a clinical and a biochemical perspective. The diagnosis of central hypothyroidism is based on low circulating levels of free T_4 in the presence of low to normal TSH concentrations. The correct diagnosis of both acquired (also termed sporadic) and congenital (also termed genetic) central hypothyroidism can be hindered by methodological interference in free T_4 or TSH measurements; routine utilization of total T_4 or T_3 measurements; concurrent systemic illness that is characterized by low levels of free T_4 and normal TSH concentrations; the use of the sole TSH-reflex strategy, which is the measurement of the sole level of TSH, without free T_4, if levels of TSH are in the normal range; and the diagnosis of congenital hypothyroidism based on TSH analysis without the concomitant measurement of serum levels of T_4. In this Review, we discuss current knowledge of the causes of central hypothyroidism, emphasizing possible pitfalls in the diagnosis and treatment of this disorder.

Central hypothyroidism is characterized by a defect in thyroid hormone secretion, resulting from the insufficient stimulation of a healthy thyroid gland by TSH[1–7]. This condition can be a consequence of an anatomic or a functional disorder of the pituitary gland and/or the hypothalamus. Central hypothyroidism was formerly termed secondary hypothyroidism of pituitary origin or tertiary hypothyroidism of hypothalamic origin, resulting from insufficient TSH stimulation by TSH-releasing hormone (TRH). These terms, however, are no longer in common use because the disorders frequently affect both the hypothalamus and the pituitary gland and the common result is defective TSH secretion[1,2].

TSH is a heterodimeric glycoprotein hormone composed of one α-subunit (TSHα) and one β-subunit (TSHβ). The hormone, which is secreted by pituitary thyrotropes, is positively controlled by TRH secreted from the hypothalamus and negatively regulated by the feedback mechanism of circulating thyroid hormones, as well as by hypothalamic secretion of dopamine and somatostatin[8]. TRH and TSH synthesis and secretion are also modulated by other factors, including corticosteroids, androgens and oestrogens[8]. Disorders affecting these regulatory control mechanisms might be involved in the pathogenesis of central hypothyroidism. Indeed, central hypothyroidism can be congenital (that is, caused by genetic defects) or acquired (that is, resulting from lesions such as tumours, traumas or cerebrovascular accidents that affect the hypothalamic–pituitary axis). In some instances, central hypothyroidism is an isolated defect of pituitary function but in most patients it occurs in combination with other pituitary hormone deficiencies. Of note, in many patients, hypothyroidism is less severe than expected and its manifestations are frequently masked by concomitant pituitary defects[6,7].

Diagnosis of central hypothyroidism is usually based on biochemical analysis — patients typically have low circulating concentrations of free T_4 associated with low to normal serum levels of TSH. However, several factors, such as the presence of concurrent systemic illness, can lead to misdiagnosis as the biochemical features of these conditions are similar to those recorded in patients with true central hypothyroidism[9–17] (TABLE 1). Levothyroxine therapy is the main treatment for central hypothyroidism (BOX 1). As with primary hypothyroidism, treatment follow-up is difficult to personalize because, in central

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Key points

- Patients with signs and symptoms of hypothyroidism, recurrent headaches or visual field defects, as well as concomitant or pre-existing hypothalamic or pituitary disorders, should be investigated for central hypothyroidism
- The presence of low levels of free T_4 with an inappropriately normal to low TSH concentration is the hallmark of central hypothyroidism, along with reduced bioactivity of circulating TSH and variable TSH response to TSH-releasing hormone (TRH) tests
- Patients who are younger than 14 years of age with central hypothyroidism accompanied by other pituitary hormone deficiencies might have a congenital form of the disease, and clinicians should screen patients for gene mutations of several pituitary transcription factors
- The diagnosis of acquired central hypothyroidism needs the careful investigation of a patient's medical history, including drug treatment, recombinant human growth hormone replacement therapy, traumatic brain injury and concomitant autoimmune diseases
- Levothyroxine therapy should only be initiated following the exclusion of adrenal insufficiency; levothyroxine replacement therapy should begin with low doses that are then slowly increased (every 3–6 weeks)
- Levels of free T_4 in the serum of patients should be maintained in the middle to upper part of the normal range, and blood should be drawn before levothyroxine administration. If serum levels of TSH are higher than 0.5 mU/l, then the patient is probably being undertreated

defects, analysis of the circulating levels of TSH is not a reliable indicator of thyroid hormone action. Therefore, the only measurement that can be used to monitor whether the dose of levothyroxine is effective remains that of circulating concentrations of free thyroid hormones, in particular, free T_4. This Review discusses our current knowledge of the causes of central hypothyroidism, emphasizing possible pitfalls in its diagnosis and treatment.

Epidemiology

The global prevalence of central hypothyroidism ranges from 1 in 20,000 to 1 in 80,000 individuals in the general population[13] and it is a rare cause of hypothyroidism (1 in 1,000 patients with hypothyroidism)[2]. The prevalence of congenital central hypothyroidism in Japan and the United States depends on the protocols adopted for screening. For example, when TSH-only-based protocols are used, congenital central hypothyroidism is often unrecognized as it is typically associated with low to normal levels of TSH in the presence of low circulating levels of free T_4. Screening programmes in Japan and the United States for congenital central hypothyroidism in neonates that included both TSH and free T_4 measurements reported a prevalence of 1 in 160,000 (REFS 18,19). Interestingly, the prevalence of congenital central hypothyroidism in the Netherlands increases to 1 in 16,000 newborn babies if the screening algorithm is based on the combined measurement of TSH, T_4 and T_4-binding globulin, which could be effective in diagnosing mild forms of the disease[16].

Although primary hypothyroidism is more commonly diagnosed in females (3.5 in 1,000) than in males (0.6 in 1,000), central hypothyroidism affects patients of all ages and both sexes equally.

Aetiopathogenesis

The aetiopathogenesis of central hypothyroidism is heterogeneous and most of the disease mechanisms remain unclear[1–3] (BOX 2; TABLE 2). In most cases of acquired and congenital central hypothyroidism, thyrotrope defects are detected in combination with other pituitary hormone deficiencies.

Defects in TSH secretion can be quantitative (that is, reduced TSH reserve), qualitative (that is, reduced bioactivity of the released TSH molecules), or both[20–27]. In the congenital forms of central hypothyroidism the defect is usually quantitative. By contrast, the defect is frequently both quantitative and qualitative in acquired central hypothyroidism. Specifically, the quantitative defect in TSH-producing cells is frequently associated with a qualitative defect in the secreted TSH isoforms that conserve immunoreactivity, but the biological activity of these isoforms and their ability to stimulate

Table 1 | **Factors that could lead to the misdiagnosis of patients with central hypothyroidism**

Factor	Comments	Refs
Methodological interference in free T_4 measurement	Many immunometric assays can give spuriously increased levels of free T_4 owing to the presence of anti-T_4 autoantibodies or abnormal transport proteins, thus masking the presence of central hypothyroidism. Only two-step assays or equilibrium dialysis seem to be reliable	9–11
Methodological interference in TSH measurement	Circulating heterophilic antibodies might interfere with TSH measurement if directed against the same species of the immunometric 'sandwich' assay antibodies, thus causing falsely increased TSH values, which might suggest primary hypothyroidism rather than central hypothyroidism	9–11
Measurement of total T_4 concentrations	Increased concentrations of thyroid hormone transport proteins (T_4-binding globulin, albumin and transthyretin) can result in increased levels of T_4, thus masking the presence of central hypothyroidism	13
Presence of concurrent systemic illness	Systemic non-thyroidal illness syndrome is characterized by low free T_4 and normal TSH concentrations, thus mimicking a non-existent state of central hypothyroidism	13
Routine use of the TSH-reflex strategy	An increasing number of laboratories use the TSH-reflex approach for screening thyroid function as a first-line test for measuring levels of TSH. It would be impossible to identify patients with central hypothyroidism using this method	14,15
Diagnosis of congenital hypothyroidism only based on TSH analysis	Without the concomitant measurement of serum T_4, congenital central hypothyroidism cannot be detected, and the consequences are dramatic for neonates with central hypothyroidism	16,17

Box 1 | **Major recommendations for the treatment of central hypothyroidism**

We recommend that the following points are considered when treating patients with central hypothyroidism. These points represent personal experience and data from the specific literature:

- Rule out the possible presence of central hypoadrenalism. Start cortisol or cortisone acetate treatment before levothyroxine therapy
- Calculate the final dose of levothyroxine based on body weight, taking into consideration the sex and age of the patient
- Start treatment with low doses of levothyroxine (25 μg per day or less taking into consideration the patient's body weight) before reaching the calculated final dose of levothyroxine
- Increase the dose every 3–6 weeks depending on the severity and duration of disease
- Remind patients that they should take the medication at least half an hour before breakfast
- Withdraw blood for testing before levothyroxine administration
- Maintain serum levels of free T_4 in the middle to upper part of the normal range

TSH receptors are severely impaired; these defects can be ameliorated with acute or chronic administration of TRH (FIG. 1).

In central hypothyroidism, the secretion of bioinactive TSH can occur following hypothalamic–pituitary tumours or injuries sustained during a breech delivery[22,25], external radiation for head tumours[26] and Sheehan syndrome[27]. The qualitative defect in TSH secretion could explain the lack of correlation between circulating levels of thyroid hormone and TSH concentrations in patients with central hypothyroidism (FIG. 2). Furthermore, the post-translational processing of TSH, particularly TSH glycosylation, is fundamental for modulating the bioactivity of TSH[21,28–30]. Impaired control of TSH synthesis and secretion by TRH, as well as other neuroendocrine or paracrine factors, could be a consequence of alterations to the post-translational processing of TSH, which could affect glycosylation and the bioactivity of the molecule[22,24,28–30].

Isolated congenital central hypothyroidism. The decreased biological activity of secreted TSH was confirmed by the biochemical and pathological characteristics of an animal affected by pure hypothalamic hypothyroidism: the TRH-knockout mouse[31]. This animal model confirmed the relevant role of TRH action in the regulation of the thyroid axis[23,24,32]. Currently, no defects in the gene that encodes TRH have been documented in humans; however, defective TRH action resulting from mutations in the gene that encodes the TRH receptor (*TRHR*) has been described in three families[33–35] (TABLE 2). Interestingly, the infancy of the patients with complete TRH resistance seemed to be uneventful and diagnosis of the male proband with homozygous *TRHR* mutations was only reached because of delayed growth at 11 years of age[34].

Mutations in *TSHB*, which encodes TSHβ, are the most frequent cause of heritable isolated central hypothyroidism[36–48]. The mutations comprise missense, truncating and intronic variants and result in abnormalities in the dimerization between TSHβ and TSHα, which prevents the production of a complete and bioactive TSH molecule. Increased circulating levels of TSHα in patients with isolated congenital central hypothyroidism — a consequence of the impaired dimerization — is pathognomonic of a *TSHB* defect[40]. Reports of *TSHB* mutations have increased over the past decade. Now, several mutations have been found that cluster in a 'hotspot' involving codon 105 in exon 3 of *TSHB* in patients of European, South American and North American descent, thus supporting the existence of a common ancestor in several of these cases[43]. Thus, along with *de novo* mutations, some mutations are genetically transmitted after first developing thousands of years ago. These mutations in *TSHB* result in a truncated TSHβ subunit lacking the so-called 'seat-belt' domain, which is involved in the stabilization of the glycoprotein hormone heterodimer[30].

In 2012, loss of function of immunoglobulin superfamily member 1 (*IGSF1*) was identified as an X-linked cause of central hypothyroidism and was found to be associated with macro-orchidism in 50% of patients[49–57]. *IGSF1* encodes the plasma membrane glycoprotein IGSF1, which is highly expressed in the pituitary and testis. Each of the identified *IGSF1* mutations impairs the proper glycosylation of IGSF1 and disrupts its trafficking to the cell surface. The variable profile of pituitary dysfunction in patients with central hypothyroidism suggests that *IGSF1* might be involved in pituitary paracrine regulation, although the specific local function of IGSF1 remains enigmatic.

In 2016, a previously unidentified mutated gene was reported to be implicated in the pathogenesis of isolated congenital central hypothyroidism[58]. Investigators identified eight patients (six men and two women) with hearing loss who had missense mutations in *TBL1X*, which encodes transducin β-like protein 1X. TBL1X is an essential subunit in the complex formed by NCOR (also known as N-CoR1) and SMRT (also known as N-CoR2), which is the major thyroid hormone receptor co-repressor involved in T_3-regulated gene expression[59]. The NCOR–SMRT complex activates the transcription of negatively regulated genes in the absence of T_3. Therefore, defects in the complex result in decreased TRH and TSHβ transcription and ultimately lead to decreased thyroid hormone synthesis and hypothyroidism.

Combined congenital central hypothyroidism. In patients with mutations in the genes that encode the pituitary transcription factors (TABLE 2), central hypothyroidism results from the inadequate differentiation of pituitary cells; these patients also have pituitary hormone deficiencies[60]. LHX3 (which is encoded by LIM homeobox protein 3 (*LHX3*)) and LHX4 are transcription factors that are involved in the early stages of pituitary development. Patients with *LHX3* mutations present with growth hormone (GH), TSH, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) deficiencies. Central hypoadrenalism is reported in some, but not all, patients. Brain-imaging studies of patients with *LHX3* mutations have shown pituitary aplasia or hypoplasia in 60% of the patients and hyperplasia in 30% of the patients[60]. Patients can also present with

Thyroid axis
Refers to the hypothalamic–pituitary–thyroid axis.

Box 2 | **Causes of acquired central hypothyroidism**

Invasive lesions
Pituitary macroadenomas, craniopharyngiomas, meningiomas, gliomas, metastases, carotid aneurysms, Rathke cleft cyst and germinoma

Iatrogenic causes
Cranial surgery or irradiation, drugs such as bexarotene, mitotane, interferon-α and oxcarbazepine

Injury
Head trauma and traumatic childbirth

Immunologic lesions
Lymphocytic hypophysitis, immunoglobulin G4 (IgG4)-related hypophysitis, treatment with anti-CTLA4 (cytotoxic T lymphocyte protein 4) antibodies (ipilimumab and tremelimumab) and anti-PIT1 (pituitary-specific positive transcription factor 1) antibody syndrome

Infarction
Post-partum necrosis (Sheehan syndrome), pituitary apoplexy and ictus

Infiltrative lesions
Sarcoidosis and iron overload (haemochromatosis and thalassaemia major) and histiocytosis X

Infectious lesions
Tuberculosis, syphilis and mycoses

extra-pituitary disorders, such as vertebral abnormalities, variable hearing alterations, and limited head and neck rotation[61]. *LHX4* mutations can lead to a variable LH to FSH ratio, as well as GH, TSH and adrenocorticotropic hormone (ACTH) deficiencies, anterior pituitary hypoplasia, hypoplastic sella turcica, cerebellar alterations and Chiari malformation[62].

Septo-optic dysplasia is characterized by the combination of optic nerve hypoplasia and/or midline forebrain defects (such as agenesis of the corpus callosum and/or absent septum pellucidum) and/or hypopituitarism associated with pituitary hypoplasia[63]. Mutations affecting *HESX1* (homeobox expressed in ES cells 1), *SOX3* (SRY-box 3) and *OTX2* (orthodenticle homeobox 2) have been reported in patients with central hypothyroidism and septo-optic dysplasia[63–65]. *HESX1* expression occurs early in the development of the pituitary placode and its reduction is necessary for *PROP1* (PROP paired-like homeobox 1) and *POU1F1* (POU class 1 homeobox 1) expression, leading to the differentiation of cells that secrete GH, TSH or prolactin[63]. Patients with homozygous mutations in these genes typically present with a severe phenotype. All patients with mutations in *HESX1*, *SOX3* and *OTX2* have GH deficiency but other pituitary deficiencies, including central hypothyroidism, are also found in 50% of patients. Optic nerve anomalies occur in 30% of patients with septo-optic dysplasia and MRI reveals pituitary hypoplasia in 80% of patients, ectopic posterior pituitary in 50–60% of patients, and corpus callosum agenesis or hypoplasia in 25% of patients[60].

Mutations affecting *SOX3* lead to X-linked hypopituitarism, ranging from isolated GH deficiency to combined pituitary hormone deficiencies, including TSH deficiency[64]. OTX2 is a paired homeodomain transcription factor that is involved in the early stages of brain development[65]. Pituitary deficiencies in patients with *OTX2* mutations range from isolated GH deficiency to panhypopituitarism. MRI shows that patients have a normal or a hypoplastic pituitary[65]. Moreover, ectopic posterior pituitary or Chiari syndrome has also been observed in these patients[65].

PROP1 is a pituitary-specific paired-like homeodomain transcription factor. Expression of PROP1 is required for the development of pituitary cells that secrete GH, prolactin and TSH. *PROP1* mutations are the most common cause of combined pituitary hormone deficiency and are associated with GH, TSH, LH, FSH, ACTH and prolactin deficiencies that can be detected from childhood to adulthood[66,67]. Neuroradiological imaging studies can show transient pituitary hyperplasia that sometimes precedes spontaneous hypoplasia[68].

POU1F1, which is required for the production of GH, prolactin and TSHβ, as well as for the expression of GH-releasing hormone receptor, is expressed fairly late during pituitary development and its expression persists in adulthood[67]. Patients with autosomal recessive and dominant *POU1F1* mutations are characterized by GH and prolactin deficiency[67,68]. By contrast, TSH deficiency can be highly variable and hypothyroidism might occur later in children of 6 to 12 years of age[68]. In all patients with POU1F1, MRI shows a normal or a hypoplastic anterior pituitary[60].

Finally, recessive mutations in *LEPR*, which encodes the leptin receptor, are a rare cause of hyperphagia and severe early-onset obesity in children. Patients might also present with central hypothyroidism of hypothalamic origin in addition to altered immune function, hypogonadotropic hypogonadism and reduced GH secretion[69–71].

Acquired central hypothyroidism. Neoplastic lesions that affect the hypothalamic–pituitary region and surgery or radiotherapy on sellar and extrasellar tumour masses are the most frequent causes of acquired central hypothyroidism[2]. The tumours most frequently involved are non-functioning pituitary adenomas[72]. Studies of patients with pituitary non-functioning macroadenomas have observed isolated or multiple pituitary deficits in 62% of patients at presentation, and 27% of patients with these tumours were reported to have central hypothyroidism[72,73]. The risk and severity of post-surgical hypopituitarism depends on tumour size, tumour extension and the experience of the neurosurgeon[74].

Craniopharyngiomas are typically slow-growing extrasellar tumours, and visual field defects and hypopituitarism are the most common presenting clinical manifestations. In children, GH deficiency, which occurs in up to 100% of patients with these tumours, is the first pituitary deficit to develop, followed by TSH deficiency (up to 25% of patients)[75]. In adults, central hypothyroidism has been described in 40% of patients, GH deficiency in 80–90%, gonadotropin deficiency in 70% and ACTH deficiency in 40%[76,77]. Surgical intervention is associated with hypopituitarism in most patients with craniopharyngiomas, whereas central hypothyroidism has been reported in 78–95% of patients with these tumours[76,77].

Table 2 | **Genetic forms of central hypothyroidism**

Gene	Phenotype	Biochemical tests
TSHB	Severe isolated central hypothyroidism of neonatal onset and pituitary hyperplasia	Levels of TSH are low or normal; levels of α-GSU are high
TRHR	Isolated central hypothyroidism with apparently uneventful infantile development and with childhood to adulthood onset (growth retardation)	• Levels of TSH are normal • TRH test shows blunted TSH or prolactin response
IGSF1	X-linked cause of central hypothyroidism deficiency syndrome. Males with *IGSF1* mutations present with increased body weight, macro-orchidism and are sometimes deficient in prolactin and GH. Delayed adrenarche and mild deficits in attentional control might also be present	Levels of TSH are normal
TBL1X	Central hypothyroidism and hearing loss	Levels of TSH are normal
LHX3	Severe central hypothyroidism with GH, prolactin, LH and FSH combined defects. Also associated with pituitary hypoplasia or hyperplasia, short or rigid cervical spine and variable deafness	TSH is detectable
LHX4	Mild to severe central hypothyroidism with GH, LH, FSH and ACTH combined defects and associated with abnormalities of cerebellum and small sella turcica	Levels of TSH are low
HESX1	Severe central hypothyroidism with combinations of deficits in GH, prolactin, LH, FSH, ACTH and vasopressin, and associated with septo-optical dysplasia, supernumerary and hypoplastic fingers	TSH is not detectable
SOX3	X-linked hypopituitarism, ranging from isolated GH to combined pituitary hormone deficiencies	Levels of TSH are low to normal
OTX2	Anophthalmia and microphthalmia. Pituitary deficit ranging from isolated GH deficiency to panhypopituitarism. Normal or hypoplastic pituitary. Ectopic posterior pituitary or Chiari syndrome might be present in these patients	Levels of TSH are low to normal
PROP1	Moderate to severe central hypothyroidism of neonatal to infantile onset, combined with GH, prolactin, LH, FSH ratio or ACTH defects, as well as pituitary hypoplasia or hyperplasia	Levels of TSH are low to normal
POU1F1	Moderate to severe central hypothyroidism of neonatal to infantile onset combined with GH and prolactin defects, prominent forehead, mid-face hypoplasia and depressed nose	Levels of TSH are low to normal
LEPR	Variable presence of central hypothyroidism combined with LH and FSH defects, severe obesity and hyperphagia	Levels of TSH are normal

α-GSU, α-glycoprotein subunit; ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; *HESX1*, homeobox expressed in ES cells 1; *IGSF1*, immunoglobulin superfamily member 1; *LEPR*, leptin receptor; LH, luteinizing hormone; *LHX3*, LIM homeobox protein 3; *OTX2*, orthodenticle homeobox 2; *POU1F1*, POU class 1 homeobox 1; *PROP1*, PROP paired-like homeobox 1; *SOX3*, SRY-box 3; *TBL1X*, trasducin β-like protein 1X; TRH, TSH-releasing hormone; *TRHR*, TRH receptor; *TSHB*, TSH β-subunit.

Direct or indirect irradiation of the hypothalamic–pituitary region can cause hypopituitarism. The risk of developing central hypothyroidism is related to both the effective dose given to the area and the total dose of radiation delivered[78,79]. Radiation-induced central hypothyroidism occurs in patients who undergo radiotherapy for pituitary tumours and craniopharyngiomas, and in 10–50% of patients who are irradiated for nasopharyngeal and paranasal sinus tumours[80,81], as well as in 12–65% of patients who are irradiated for brain tumours of any site[82,83]. Radiosurgery, however, might reduce the risk of hypopituitarism and central hypothyroidism. Data from two studies suggest that Leksell gamma knife or stereotactic linear accelerator radiosurgery result in fewer cases of hypopituitarism, including central hypothyroidism, than radiotherapy[84,85].

Various drugs can induce transient and usually reversible forms of central hypothyroidism[86]. High doses of neurotransmitters, such as somatostatin and dopamine, can block the secretion of TSH for a brief period of time. Normal TSH secretion is promptly resumed, however, through the negative feedback mechanism that is activated following a decrease in levels of thyroid hormones[86]. Other drugs, such as mitotane (for treating adrenal cancer)[87], interferon-α (for treating chronic hepatitis C infection)[88] and oxcarbazepine (for treating epilepsy)[89] can also induce central hypothyroidism. Retinoid X receptor agonists such as bexarotene are useful in patients with certain malignancies but even a single dose of bexarotene can cause central hypothyroidism in some patients with advanced cancer[90].

Patients with traumatic brain injury can develop hypopituitarism; the prevalence of anterior pituitary dysfunction is 15–68% in patients with traumatic brain injury[91]. The prevalence of central hypothyroidism in these patients varies between series from 5% to 29%[91,92], a discrepancy that could result from the timing of testing or from the diagnostic procedure used to identify pituitary hormone

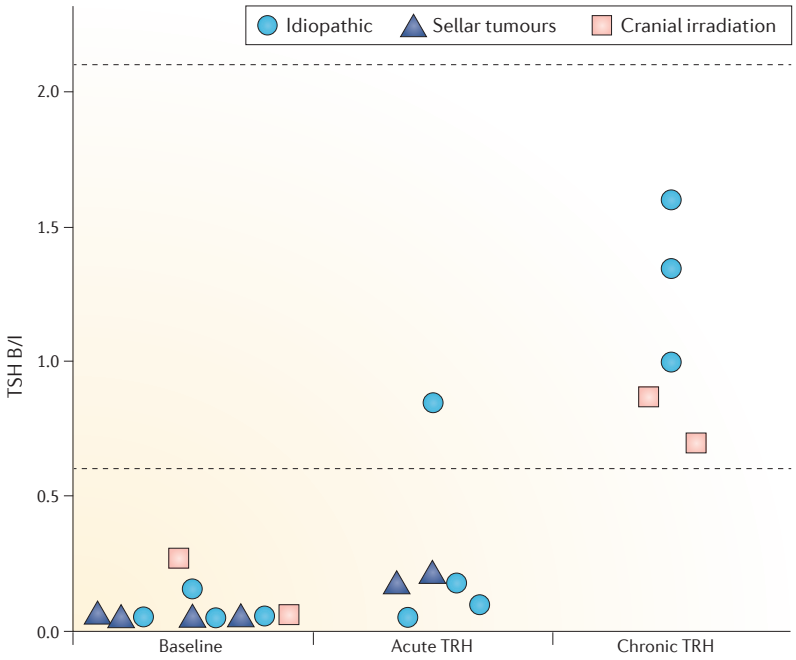

Figure 1 | **Measurement of the ratio between TSH bioactivity and TSH immunoreactivity (TSH B/I) in sera from patients with central hypothyroidism of hypothalamic origin.** At baseline, TSH from all patients had undetectable basal bioactivity (TSH B/I < 0.2), which normalized in only one patient after acute TSH-releasing hormone (TRH) administration but which normalized in all patients after chronic TRH administration. The area between the dashed lines represents the normal range of TSH B/I.

deficiencies. Subarachnoid haemorrhage or cerebral infarcts can induce hypopituitarism, albeit rarely, with central hypothyroidism diagnosed in <2% of patients[93].

Granulomatous diseases, which include sarcoidosis, tuberculosis, histiocytosis X and haemochromatosis (iron overload), can also induce hypopituitarism and central hypothyroidism by directly acting on the pituitary stalk[94,95]. In the context of central hypothyroidism, infiltration and destruction of the pituitary stalk prevent the normal release of neurohormones to pituitary cells and cause pituitary hormone deficit.

Hypophysitis is a condition that is characterized by lymphocytic infiltration of the pituitary gland. Based on histopathological features, the disease can be classified as lymphocytic or granulomatous[96–98]. Hypopituitarism is the most prevalent feature of lymphocytic hypophysitis, and central hypothyroidism is the pituitary hormone deficiency that is most frequently diagnosed after central hypoadrenalism and hypogonadotropic hypogonadism[96]. Xanthogranulomatous hypophysitis is a very rare form of pituitary hypophysitis (<1% of patients)[96]. Xanthogranulomatous hypophysitis has three forms: primary, secondary and a component of multiorgan systemic disease, such as tuberculosis, sarcoidosis and granulomatosis. Indeed, primary xanthogranulomatous hypophysitis has an autoimmune aetiology, and secondary xanthogranulomatous hypophysitis is a reactive degenerative response to an epithelial lesion, such as craniopharyngiomas, Rathke cleft cyst, germinoma and pituitary adenomas.

An example of a multiorgan systemic disease that results in xanthogranulomatous hypophysitis is immunoglobulin G4 (IgG4)-related hypophysitis, which is a clinical entity that is characterized by IgG4-positive plasma cell and lymphocyte infiltration and elevated serum concentrations of IgG4, and is frequently diagnosed as a component of IgG4-related disease[99]. Anti-CTLA4 (cytotoxic T lymphocyte protein 4) antibody treatments, such as ipilimumab and tremelimumab, are prescribed for several types of cancer but one study has reported that their use resulted in the appearance of hypophysitis in up to 10% of treated patients[100]. Most patients with ipilimumab-induced hypophysitis were reported to have multiple anterior pituitary hormone deficiencies. In these patients, central hypothyroidism was the most frequently reported form of hypophysitis (up to 90% of cases), followed by central adrenal insufficiency and hypogonadotropic hypogonadism[101].

Finally, central hypothyroidism has been reported in adult patients following the development of GH, prolactin and TSH deficiencies and the presence of detectable circulating anti-PIT1 (pituitary-specific positive transcription factor 1) antibodies, the so-called anti-PIT1 antibody syndrome[102].

Clinical and biochemical presentation

The clinical features of central hypothyroidism with which a patient presents depend on the aetiology, severity of the hypothalamic–pituitary impairment, extent and severity of associated hormone deficiencies, and the age of the patient at the time of disease onset. Congenital central hypothyroidism is clinically more severe than the acquired forms[67,68]. The symptoms and signs of central hypothyroidism, which include fatigue, depression, cold intolerance, hoarseness, dry skin, constipation, bradycardia and hyporeflexia, are usually the same but milder than those of primary hypothyroidism, and goitre is seldom present. Some studies have suggested that residual thyrotroph function, as well as the physiological constitutive activity of the TSH receptor, in patients with central hypothyroidism might explain this discrepancy[103,104]. In the presence of combined pituitary deficiencies, other endocrine manifestations, for example, growth failure, delayed puberty, adrenal insufficiency and diabetes insipidus, lead the patients to seek medical attention before their hypothyroidism manifests[105].

As in patients with primary hypothyroidism, untreated central hypothyroidism can have adverse cardiovascular consequences, so patients should undergo appropriate monitoring for these effects[106]. Doppler is a sophisticated method to explore cardiac function and thus is useful to record even minimal signs of disorders that might be secondary to central hypothyroidism. Doppler echocardiography seems to be useful not only for the collection of myocardial performance indexes and the diagnosis of cardiovascular disorders, but also for the recognition of preclinical central hypothyroidism[107]. Further studies are needed to improve how we identify and treat patients with central hypothyroidism. Studies in families with genetic forms of central hypothyroidism would be particularly useful.

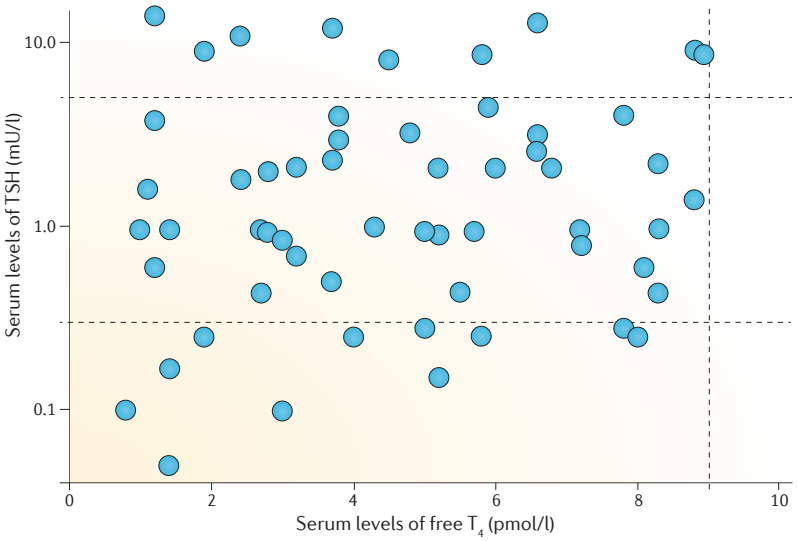

Figure 2 | **Serum levels of TSH and free T_4 in a large series of patients with central hypothyroidism investigated in our institution.** Serum levels of TSH (logarithmic scale) and free T_4 in a large series of patients with central hypothyroidism investigated at Ospedale Maggiore Policlinico, Milan, Italy. Each blue circle represents one patient, and the area between the dashed lines represents the normal range of TSH (mU/l) and free T_4 (pmol/l) in the serum. The lack of correlation between the levels of TSH and free T_4 is consistent with the reduced bioactivity of circulating TSH molecules. Data from REF. 25.

Patients with congenital central hypothyroidism present with various syndromic and complex clinical features depending on the genes involved[60] (TABLE 2). In patients with *TSHB* mutations, central hypothyroidism is clinically undetectable at birth. Biochemically, after 8 weeks of age, these patients have raised serum levels of α-GSU (α-glycoprotein subunit) and an impaired TSH response to TRH stimulation, and they are characterized by severe signs and symptoms of the disease[40]. In these patients, prolactin secretion is normal and fully responsive to TRH stimulation[40].

Central hypothyroidism that is characterized by the absence of a TSH and prolactin response to TRH is caused by inactivating mutations in the gene that encodes the TRH receptor[33–35]. In the first reported cases of this form of central hypothyroidism, the clinical manifestations were mild (including growth retardation and delayed bone age) despite evidence of reduced serum concentrations of free T_4. Surprisingly, despite the late administration of treatment, no neurological deficits were found in any patients, suggesting that sufficient levels of thyroid hormone were produced during childhood. Importantly, T_4 replacement was reported to be effective in improving growth and quality of life in these individuals[33,34]. Interestingly, although the TRH receptor is expressed on lactotrophs and mediates prolactin secretion in response to exogenous TRH, a woman with a homozygous nonsense *TRHR* mutation (p.Arg17*) had two successful pregnancies and lactated normally[33].

A loss-of-function mutation in *IGSF1* is an X-linked cause of central hypothyroidism. A multicentre study published in 2013 analysed all clinical and biochemical characteristics associated with IGSF1 deficiency. The authors reported that, in male patients, central hypothyroidism was associated with hyperprolactinaemia in 67% of patients, with transient GH deficiency in 13% of cases, and occasionally with macro-orchidism (50% of cases)[56]. Puberty has also been reported to be delayed in patients with IGSF1 deficiency, including the growth spurt and pubic hair development; however, testicular growth starts at a normal age[57]. Notably, BMI, body fat percentage and waist circumference are increased, and most male patients >55 years of age have metabolic syndrome[56]. In heterozygous female carriers of this loss-of-function mutation, 33% develop central hypothyroidism and, as observed in affected males, BMI, body fat percentage and waist circumference are higher than in non-carrier women. Finally, mild neurological phenotypes in the affected men, such as hypotonia, delayed psychomotor development, clumsy behaviour and attention deficit disorder, have been described in some adult patients[52]. Patients with *TBL1X* mutations present with central hypothyroidism that is associated with hearing loss[58].

Central hypothyroidism is usually diagnosed by measuring circulating levels of T_4 (FIG. 3), as the condition is difficult to recognize clinically. Direct two-step methods are used to biochemically analyse each patient's levels of free T_4, after ruling out factors interfering with the immunometric assays, such as thyroid autoantibodies or abnormal binding proteins[9,12]. A number of additional factors can prevent the correct diagnosis of acquired and congenital central hypothyroidism (TABLE 1). Moreover, serum levels of TSH are usually low to normal, or even slightly elevated, in patients with tertiary (hypothalamic) hypothyroidism. Tertiary hypothyroidism can be misdiagnosed as a condition of primary hypothyroidism[12]. Therefore, measurement of circulating anti-thyroid autoantibodies and thyroid ultrasonography should be carried out in every patient with central hypothyroidism[107]. Finally, care must be taken not to confuse the physiological decrease in free T_4 during pregnancy with central hypothyroidism, unless the patient has a hypothalamic–pituitary disorder[7].

A TRH stimulation test, which involves the intravenous administration of 200 μg TRH, has been proposed as a method to differentiate pituitary from hypothalamic central hypothyroidism. Pituitary central hypothyroidism is characterized by an exaggerated (delayed) and/or long TSH response, which is impaired in hypothalamic central hypothyroidism[3]. The practical utility of the TRH test, however, is limited as the pituitary and the hypothalamus can be simultaneously involved in acquired central hypothyroidism. Importantly, absent or impaired free T_4 and free T_3 responses, measured at both 120 min and 180 min after TRH injection, indirectly indicate the secretion of bioinactive TSH (FIG. 4).

Indeed, a 10% variation in the levels of free T_4 might be considered as normal in euthyroid patients[108]. Therefore, in patients being followed up for pituitary diseases, a greater than 20% decrease in circulating levels of free T_4 might suggest central hypothyroidism, even if serum concentrations of free T_4 are still in the normal range[108].

Immunometric assays
Methods involving antibody–antigen binding reactions, based on the law of mass action.

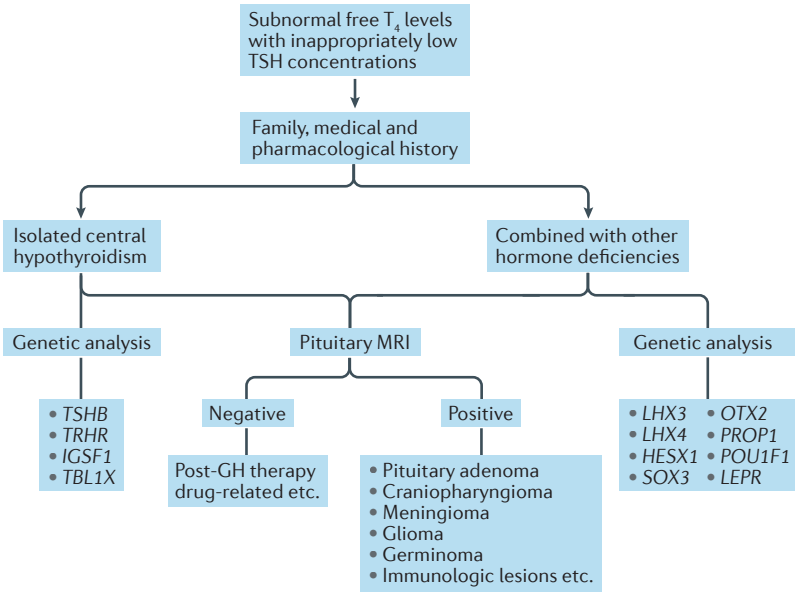

Figure 3 | **Proposed algorithm for the diagnosis of the different forms of central hypothyroidism.** GH, growth hormone; *HESX1*, homeobox expressed in ES cells 1; *IGSF1*, immunoglobulin superfamily member 1; *LEPR*, leptin receptor; *LHX3*, LIM homeobox protein 3; *OTX2*, orthodenticle homeobox 2; *POU1F1*, POU class 1 homeobox 1; *PROP1*, PROP paired-like homeobox 1; *SOX3*, SRY-box 3; *TBL1X*, trasducin β-like protein 1X; *TRHR*, TSH-releasing hormone receptor; *TSHB*, TSH β-subunit. Adapted from REF. 2, Macmillan Publishers Limited.

Patients with non-thyroidal illness syndrome, a fairly common finding following any acute or chronic illness, such as starvation, sepsis, myocardial infarction and renal disease[109–111], have thyroid function values that considerably overlap with those of patients who have central hypothyroidism[12,112–114]. Non-thyroidal illness syndrome might result from factors such as the downregulation of TRH expression in neurons in the paraventricular nucleus[115], reduced TSH secretion and modifications in thyroid hormone metabolism[116]. Clinicians need to be aware of this transient phenomenon and consider biochemical data in the context of clinical status in order to avoid inappropriate treatment[117]. In this respect, a clue to distinguish central hypothyroidism from non-thyroidal illness syndrome is the evaluation of serum levels of free T_3, which are reduced in non-thyroidal illness syndrome but which are normal in mild to moderate forms of central hypothyroidism.

An MRI assessment of the pituitary and an evaluation of the hypothalamic–pituitary axis should be considered following the biochemical diagnosis of central hypothyroidism if a family history of central hypothyroidism is confirmed, if a suggestive clinical history including head trauma, subarachnoidal haemorrhage, previous brain irradiation or surgery is confirmed, or if specific symptoms such as headaches or visual field defects are confirmed.

Treatment and follow-up

As with primary hypothyroidism, the aim of central hypothyroidism treatment is the restoration and maintenance of euthyroidism[118]. With this goal in mind, levothyroxine replacement therapy is recommended, as no evidence supports the superiority of combined treatment with levothyroxine and liothyronine in either adults or children[119–123].

A consensus has not been reached regarding the evaluation of the adequacy of the levothyroxine dose in central hypothyroidism because, unlike in primary hypothyroidism, serum levels of TSH cannot be used to monitor patient progress. In fact, TSH secretion is suppressed even during low-dose levothyroxine treatment, a finding that could be related to the negative feedback of circulating hormones on residual thyrotrophs[108,124]. Research suggests that in most patients with central hypothyroidism, TSH is suppressed during levothyroxine treatment even though serum levels of free T_4 are still in the hypothyroid range[124]. These data suggest that the normal serum levels of TSH during levothyroxine treatment reflect the possible undertreatment of central hypothyroidism. In particular, data show that levels of TSH above 1.0 mU/l should be considered a sign of insufficient replacement in patients with central hypothyroidism[124].

Indeed, most of the research published since 2011 investigating levothyroxine replacement therapy in patients with central hypothyroidism has underlined the pitfalls in achieving optimal replacement[118]. In particular, by comparing free T_4 values in these groups of patients with those found in patients with primary hypothyroidism and adequately treated with levothyroxine, investigators have demonstrated that patients with central hypothyroidism are commonly undertreated[125]. In general, the assumption is that serum levels of free T_4 in the middle to upper part of the normal range represent an appropriate target in patients with central hypothyroidism who are treated with levothyroxine[107,122,125,126].

During follow-up, blood samples for measuring levels of free T_4 must be drawn before the ingestion of levothyroxine tablets. Finally, biochemical indices of thyroid hormone action at the tissue level, such as sex-hormone-binding globulin and carboxy-terminal telopeptide of type 1 collagen, are of little help in monitoring levothyroxine treatment in central hypothyroidism because all of these parameters can be affected by the coexistence of alterations in adrenal, somatotroph or gonadal function[108].

Levothyroxine treatment should be started at a low daily dosage of 25 μg and then gradually increased by 25 μg every 2–3 weeks to reach the full replacement dose (from 1.3 ± 0.3 μg/kg of bodyweight to 1.6 ± 0.5 μg/kg of bodyweight per day), which is similar to that used for primary hypothyroidism[3,107,126]. For patients with central hypothyroidism, the levothyroxine dose varies depending on concomitant treatment (such as oestrogens and recombinant human GH (rhGH)), sex and age, with an increased dose required in the young[127,128]. Of crucial importance, levothyroxine treatment in children should be started as early as possible with full-replacement doses in order to prevent serious brain damage[17].

GH deficiency can mask subclinical forms of central hypothyroidism that only become apparent following the initiation of rhGH replacement therapy[129–133]. rhGH administration has been found to enhance peripheral deiodination of T_4 to T_3 (REF. 134). This effect on

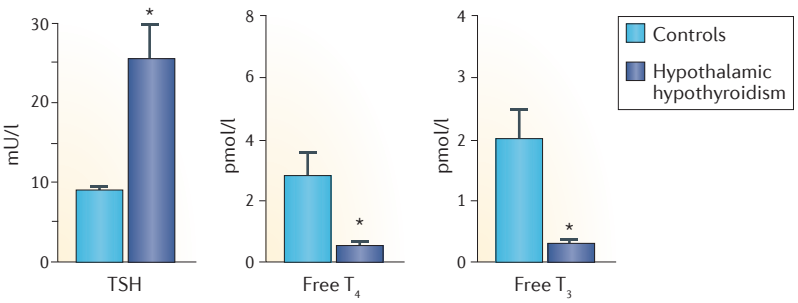

Figure 4 | **TRH stimulation test in controls and in patients with hypothalamic hypothyroidism.** Net increments of serum levels of TSH, free T_4 and free T_3 after a TSH-releasing hormone (TRH) stimulation test in patients with central hypothyroidism of hypothalamic origin and controls matched for age and sex. Note the exaggerated TSH response and the significantly smaller increase in free T_4 and free T_3 in hypothalamic hypothyroidism. These results provide an indirect estimate of the poor bioactivity of TSH molecules secreted in these conditions. the asterisks indicate a highly significant difference ($P < 0.001$) between patients and controls. Adapted from Persani, L. & Beck-Peccoz, P. in *Werner and Ingbar's the Thyroid: a Fundamental and Clinical Text* 10th edn (eds Braverman L. E. & Cooper D.) 560–568. (Lippincott Williams, Wilkins, 2012).

T_4 metabolism is biologically relevant only in patients with combined pituitary hormone deficiencies and a partial impairment of thyrotroph function[129,132,133]. In fact, contrary to observations in patients with multiple pituitary hormone deficiencies, rhGH replacement therapy does not induce central hypothyroidism in children with idiopathic isolated GH deficits[132]. In this setting, slow growth, despite adequate rhGH substitution and normal levels of insulin-like growth factor 1, is an important clinical marker of central hypothyroidism. Therefore, strict monitoring of thyroid function is mandatory when treating children with multiple pituitary hormone deficiencies[131,132].

On a final note, clinicians should always exclude concomitant central adrenal insufficiency before initiating levothyroxine therapy because the restoration of euthyroidism might precipitate an adrenal crisis in a patient with unrecognized central hypoadrenalism[5,6]. In fact, the normalization of thyroid function increases cortisol metabolism in these patients, thereby leading to a greater glucocorticoid requirement[130]. If adrenal function cannot be evaluated before starting levothyroxine treatment, then prophylactic treatment with steroids, such as hydrocortisone or cortisone acetate, should be considered[2,3].

Conclusions

Although our knowledge of the causes of central hypothyroidism is increasing, several familial cases and acquired cases (possibly related to specific antithyrotroph autoantibodies) classified as idiopathic remain unexplained. Patients with central hypothyroidism typically present with mild symptoms, but diagnosing the disease can be complicated by biochemical interference. The treatment of central hypothyroidism is based on levothyroxine supplementation (BOX 2). In order to accurately evaluate the adequacy of the treatment, serum concentrations of free T_4 should be measured in blood withdrawn before levothyroxine administration. In this respect, we recommend a clinical target for serum levels of free T_4 in the middle to upper part of the normal range. Further studies, however, are needed to better understand thyroid hormone metabolism and action at the tissue level. Moreover, if research efforts could identify specific markers for treatment then we would be able to provide patients with a more precise and personalized replacement therapy than is currently possible.

When managing patients with central hypothyroidism, clinicians should consider the possible interplay between central hypothyroidism treatment and any potential coexisting pituitary hormone deficiencies. In particular, it is crucial to exclude concomitant central adrenal insufficiency before the initiation of levothyroxine therapy.

Finally, although relevant progress has been made using new molecular biology techniques in recognizing the genes involved in the aetiology of central hypothyroidism, several cases of congenital origin remain unexplained. Moreover, the efficacy of levothyroxine substitutive therapy is still mainly based on the measurement of free T_4 and puzzling clinical symptoms. A future more detailed understanding of thyroid hormone metabolism and action in various tissues will disclose novel and more specific indicators of a proper levothyroxine replacement. It has been demonstrated that mouse embryonic stem cells can be induced to differentiate into thyroid follicular cells *in vitro* and generate functional thyroid tissue[135]. Therefore, the application of stem cell technologies in the treatment of both primary and central hypothyroidism, an area that so far received relatively little attention in regenerative medicine, might be foreseeable in the not too distant future.

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Competing interest statement
The authors declare no competing interests.

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ORIGINAL ARTICLE

The relationship between quality of life, cognition, and thyroid status in Graves' disease

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Summary

Purpose To assess quality of life (QoL) and cognitive function among Graves' disease (GD) patients with different thyroid status, with and without ophthalmopathy.

Methods This is a cross-sectional clinic-based study involving 154 patients with GD (81.27% were female, mean age 45.6 ± SD 11.2 years) and 54 (35.06%) had ophthalmopathy. Data were collected after an informed consent from all patients was obtained. All patients completed the 36-Item Short Form Health Survey and Mini-Mental State Examination. Patients with ophthalmopathy also completed the Graves' Orbitopathy Quality of Life Questionnaire.

Results Patients with hyperthyroidism presented a greater impairment in QoL when compared to euthyroidism group. A lower score in physical role functioning was found in both subgroups with active disease (hyperthyroidism and euthyroidism using thionamides). A lower score was also seen in visual function, only in patients with hyperthyroidism, without difference in appearance. No difference was found in cognition between patients. Younger ages at diagnosis, male sex, euthyroidism and absence of ophthalmopathy were factors associated with better QoL, as well as a shorter disease duration was associated with better recall, attention and calculation.

Conclusions An impairment in QoL among patients with active GD was evidenced, even in those receiving thionamides and in euthyroidism. Ophthalmopathy was a factor associated with a poor QoL and no clear evidence of cognitive impairment was demonstrated.

Keywords Graves' disease · Graves' ophthalmopathy · Quality of life · Cognitive function · Hyperthyroidism

Introduction

Graves' disease (GD) is an autoimmune disorder characterized by glandular hyperfunction and excess of thyroid hormones, associated with loss of the negative feedback between thyroid and hypothalamic-pituitary axis. It is the most common cause of hyperthyroidism, is more commonly found in young and female patients [1, 2].

Thyroid hormones play an essential role in mood regulation and cognition, with a great clinical variability that is directly related to disease duration, thyrotoxicosis severity, individual susceptibility to thyroid hormone excess and patient's age [3, 4]. In the acute phase of GD, patients usually complain of poor concentration and memorization, emotional lability, irritability, insomnia, psychomotor agitation, depression, and anxiety. Some prospective studies have shown that both affective and cognitive symptoms presented at the onset of the condition usually improve after reaching euthyroidism [5], however a Swedish and a Danish prospective study showed that the impairment in quality of life persists even after months and years of euthyroidism [6, 7].

Besides poor quality of life-related to hyperthyroidism, Graves' disease patients with involvement of the eyes have an additional negative impact on psychological, social and work efficiently, which affect the quality of life and is associated with great changes in physical appearance [8]. Previous studies have reported a significantly reduced quality of life and an increased psychosocial morbidity in patients with ophthalmopathy, especially those with severe or active ophthalmopathy [9, 10].

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Most studies that evaluated the quality of life in patients with GD were limited to analyze the subgroup affected by ophthalmopathy, with few studies directed to an overall evaluation of the patient, including cognitive status. Thus, the impact of GD on patient well-being cannot be neglected, regardless of disease state and whether the individual has ocular involvement or not.

Therefore, the objective of this study is to evaluate the quality of life and cognitive function in GD patients according to the status of thyroid function and regarding the different therapeutics options, with and without ocular disease.

Materials and methods

Patients recruitment

The study is a cross-sectional clinic-based study involving selected GD patients followed at the Thyroid Disease Unit in a tertiary Endocrinology Department. The diagnosis of GD was based on signs and symptoms of thyrotoxicosis, suppressed level of thyroid stimulating hormone (TSH), high level of free thyroxine (fT4) and presence of TSH receptor antibodies (TRAb). One hundred and fifty-four patients with GD older than 18-year-old were studied (29 men and 125 women, mean age 45.6 ± SD 11.2 years and mean duration of the disease 8.0 ± 6.5 years). To evaluate the influence of thyroid hormones on quality of life and cognition, patients were divided into two groups according to TSH and fT4 levels to determine if the patients were in hyperthyroidism or euthyroidism. To evaluate the repercussion of treatment choice in quality of life and cognition, they were also subdivided into 5 subgroups according to thyroid status and therapeutic option employed during follow up. Groups were respectively: hypothyroidism after radioiodine therapy using levothyroxine with normal thyroid function, hypothyroidism after thyroidectomy using levothyroxine with normal thyroid function, active GD using thionamides with normal thyroid function, active GD using thionamides or not and with hyperthyroidism and disease remission.

Patients were excluded from the study if they showed any acute inflammatory disease, history of recent cardiovascular events (myocardial ischemia, unstable angina or stroke), malignant neoplasia, heart failure (NYHA III or IV), severe hepatic disease, severe kidney disease (CKD stages 4, 5, and hemodialysis), hepatitis B, C and HIV infection, psychiatric disease, cognitive dysfunction or preexistence dementia and functional illiterate. Also, were excluded patients presenting comorbidities that interfere in the quality of life as disabling rheumatoid arthritis, severe obesity or diabetes (type 1 or 2) with inadequate glycemic control.

Data were collected from October 2015 to October 2018, and all participants gave their written informed consent and ethical committee approval for the study was obtained according to Declaration of Helsinki, Human Research Ethics Committee in Lausanne, No 204/14). Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient. CAAE: 47834815.0.0000.5404.

Clinical assessment

Clinical characteristics, images, and biochemical data were obtained from medical records. Clinical data collected were: age at diagnosis, disease duration, gender, years of schooling, comorbidities (including other autoimmune or chronic disease), smoking habits, use of levothyroxine and methimazole, radioiodine therapy, thyroid ultrasound characteristics, weight, height, body mass index, ophthalmometry (right and left eye), follow-up, and estimated time of thyrotoxicosis and euthyroidism (based on medical appointment). Serum TSH (reference values 0.41–4.5 mUI/L), fT4 (reference values 0.9–1.8 m/dL), thyroglobulin antibodies (reference values < 115 mUI/L), thyroid peroxidase antibodies (reference values < 35 UI/mL) and TRAb (reference values < 1.58 UI/mL) were measured by electrochemiluminescence immunoassay.

Clinical eye evaluation was elaborated to define the degree of ophthalmopathy inflammatory activity and the measure of proptosis. Clinical Activity Score (CAS) assessed the degree of inflammation and was calculated from 7 items, with 1 point assigned to each alteration presented: spontaneous orbital pain, gaze-evoked orbital pain, eyelid swelling, eyelid erythema, conjunctival redness, chemosis and inflammation of caruncle or plica. A CAS of 3 or higher indicates an active inflammatory ophthalmopathy.

Proptosis was evaluated with an ophthalmometer routinely used in our service. It is an instrument composed of a lateral rod with marking in centimeters as a ruler that connects to a front rod, forming an angle of 90°. The lateral rod is adjusted to the temporal region of the patient, and then it is possible to measure the distance between the outer corner of the eye and the cornea.

Health-related quality of life was assessed using a Brazilian version of the 36-Item Short Form Health Survey (SF-36) questionnaire which includes subscales for physical function, limitations due to both health and emotional problems, pain, general health, vitality, social function, and general mental health. These eight domains are summarized in Physical Component Scale and Mental Component Scale. Answers were calculated into scores ranging from 0 (worst) to 100 (best). We did not use a specific questionnaire for quality of life for patients with thyroid disease because there

was no such measure validated for use with Brazilian patients at the time of our study.

Cognition was assessed using the Mini-Mental State Examination (MMSE) which is a 30-point questionnaire used to measure cognitive impairment. The test takes between 5 and 10 min and examines functions including registration, attention and calculation, recall, language, ability to follow simple commands and orientation. Any score higher than or equal to 24 points (out of 30) indicates a normal cognition. Below these 24 points, patients are characterized as having a mild (19–23 points), moderate (10–18 points) and severe cognitive impairment (≤9 points).

Patients with ophthalmopathy were also evaluated with Graves' Orbitopathy Quality of Life Questionnaire (GO-QoL). The GO-QoL contains 8 questions on visual functioning and 8 questions on appearance; answers were calculated into scores ranging from 0 (worst) to 100 (best).

All the subjects were evaluated in a calm and quiet room, with no interference from the outside. They had enough time to answer all the questionnaires. The three instruments were applied at the same day, one followed by the other, by the same physician.

Statistical analyses

Statistical analyses were performed with the Statistical Analysis System (SAS)—System for Windows, version 9.4. SAS Institute Inc., 2002–2008, Cary, NC, USA. To describe sample profile according to the study variables, frequency tables of categorical variables with absolute (n) and percentage (%) values were used, and descriptive statistics of numerical variables, with mean values, standard deviation, minimum and maximum values and median. The Mann–Whitney test was used to compare cognitive function and quality of life. The Kruskal–Wallis test was used to compare cognitive function and quality of life between all groups, followed by Dunn's post-hoc test to identify the differences. The Spearman correlation coefficient was used to correlate fT4 and TSH with cognitive function and quality of life. A linear regression analysis was used to correlate factors with cognitive function and quality of life. The data were transformed into ranks. The significance level was set at $p < 0.05$.

Results

Demographic and clinical characteristics

We analyzed 154 GD patients, of which 125 (81.17%) were female and 54 (35.06%) had ophthalmopathy, 41 (26.62%) were smokers. Mean age at diagnosis, age at evaluation, disease duration and years of schooling were respectively: 37.49 ± 11.45; 45.6 ± 11.2; 8.18 ± 6.51; and 8.01 ± 3.53. Patients were divided into two groups, according to thyroid status at the evaluation and then subdivided into five subgroups, according to thyroid function and treatment employed. Of these, 128 (83.12%) subjects were in euthyroidism and 26 (16.88%) were in hyperthyroidism at the time of the evaluation. Subgroups were, respectively: 58 (37.66%) at hypothyroidism after radioiodine therapy using levothyroxine with normal thyroid function, 20 (12.99%) at hypothyroidism after thyroidectomy using levothyroxine with normal thyroid function, 27 (17.53%) at active GD using thionamides with normal thyroid function, 26 (16.88%) at active GD using thionamides or not and with hyperthyroidism and 23 (14.94%) at disease remission.

Table 1 Frequencies of baseline characteristics of patients

Variables	Frequency $N = 154$
Sex (Female/Male)	81.17 / 18.83%
Smoking	26.62%
Ophthalmopathy	35.06% (54)
CAS 0	9.25% (5)
CAS 1–2	75.92% (41)
CAS ≥ 3	14.81% (8)
CAS subitem's	
Spontaneous orbital pain	0
Gaze-evoked orbital pain	1.85% (1)
Eyelid swelling	14.81% (8)
Eyelid erythema	50% (27)
Conjunctival redness	90.74% (49)
Chemosis	1.85% (1)
Inflammation of caruncle or plica	11.11% (6)
Other chronic disease*	51.30%
Other autoimmune disease**	20.25%
TgAb > 115 mUI/L	46.34%
TPOAb > 35 UI/mL	70.63%
Thyroid status at the evaluation	
Hyperthyroidism	16.88%
Euthyroidism	83.12%
Subgroups	
Hypothyroidism after radioiodine therapy	37.66%
Hypothyroidism after thyroidectomy	12.99%
Active disease with normal thyroid function under thionamides	17.53%
Active disease with hyperthyroidism	16.88%
Disease remission	14.94%

Values are expressed as n (%)

CAS Clinical Activity Score, *TbAB* thyroglobulin antibodies, *TPOAb* thyroid peroxidase antibodies, *N* number

*Hypertension, diabetes, dyslipidemia, and obesity

**Type 1 diabetes, vitiligo, psoriatic arthritis, systemic lupus erythematosus, and rheumatoid arthritis

Table 2 Descriptive analysis of clinical and laboratory characteristics of patients

Variables	Mean ± SD $N = 154$
Age at diagnosis (years)	37.49 ± 11.45
Age at the evaluation (years)	45.67 ± 11.21
Thyroid disease duration (years)	8.18 ± 6.51
Years of schooling (years)	8.01 ± 6.51
Body Mass Index (Kg/m^2)	27.69 ± 4.76
Proptosis of the right eye (mm)	13.50 ± 4.11
Proptosis of the left eye (mm)	13.67 ± 4.21
Estimated time of thyrotoxicosis (months)	27.01 ± 19.44
Estimated time of euthyroidism (months)	59.48 ± 57.39
TSH at the evaluation (mUI/L)	2.04 ± 1.55
fT4 at the evaluation (m/dL)	1.61 ± 1.04
Follow-up (months)	73.34 ± 64.19

Values are expressed as mean and SD

mm millimeters, *TSH* thyroid stimulating hormone, *fT4* free thyroxine, *SD* standard deviation, *N* number

Clinical and biochemical characteristics are summarized in Tables 1 and 2.

Quality of life in Graves' disease patients according to the disease status and presence of ophthalmopathy

When comparing patients with hyperthyroidism and euthyroidism, it is possible to state that: hyperthyroidism group showed a greater impairment in quality of life, especially in physical role functioning (59.62 vs. 82.81; $p = 0.006$) and emotional role functioning (61.54 vs. 82.81; $p = 0.009$) (Table 3). Analyzing patients in relation to the current situation of the disease and type of treatment employed, we also found a lower score in physical role functioning, at both subgroups with active disease, in hyperthyroidism and euthyroidism using thionamides ($p = 0.028$) (Table 4).

At evaluation of patients with ophthalmopathy by Graves' Orbitopathy Quality of Life Questionnaire (GO-QoL), a greater impairment of visual function was seen among patients with hyperthyroidism when compared to euthyroidism group (88.93 vs. 95.17; $p = 0.026$), but no difference was found in appearance (53.98 vs. 66.70; $p = 0.177$). No difference in visual function ($p = 0.1637$) and appearance ($p = 0.5714$) was found when they were compared into subgroups of treatment.

At multiple logistic regression analysis of the variables, thyroid status (euthyroidism or hyperthyroidism), age at diagnosis, age at evaluation, disease duration, sex, ophthalmopathy, years of schooling, estimated time of thyrotoxicosis and euthyroidism, showed that factors associated with better quality of life were younger ages at diagnosis (physical functioning, $p = 0.009$; physical role functioning, $p = 0.002$; social role functioning, $p = 0.035$ and emotional role functioning, $p = 0.002$), male sex (pain, $p = 0.0464$ and mental health, $p = 0.0039$) patients in euthyroidism (physical role functioning, $p = 0.005$ and emotional role functioning, $p = 0.001$) and absence of ophthalmopathy (general health perception, $p = 0.0257$; social role functioning, $p = 0.0337$ and mental health, $p = 0.0165$).

Table 3 36-Item Short Form Health Survey (SF-36) and Graves' Orbitopathy Quality of Life Questionnaire comparing Graves' disease patients in hyperthyroidism and euthyroidism at the evaluation

	Hyperthyroidism	Euthyroidism	*p*-value
36-Item Short Form Healthy Survey (SF-36)			
Physical functioning*	85.38 ± 21.91	92.07 ± 12.53	0.476
Physical role functioning*	59.62 ± 47.47	82.81 ± 35.87	**0.006**
Bodily pain*	72.12 ± 30.33	70.26 ± 26.24	0.692
General health perception*	66.31 ± 28.62	74.13 ± 23.92	0.179
Vitality*	70.58 ± 27.14	73.20 ± 22.53	0.874
Social role functioning*	94.17 ± 12.34	91.31 ± 18.60	0.558
Emotional role functioning*	61.54 ± 47.79	82.81 ± 36.70	**0.009**
Mental health*	69.23 ± 25.84	73.86 ± 25.12	0.474
Physical component scale*	48.82 ± 9.76	51.33 ± 6.67	0.614
Mental component scale*	49.10 ± 10.49	51.66 ± 11.30	0.240
Graves' Orbitopathy Quality of Life Questionnaire (GO-QoL)			
Visual Function	88.93 ± 9.27	95.17 ± 7.11	**0.026**
Appearance	53.98 ± 25.81	66.72 ± 12.5	0.177

Values are expressed as mean and standard deviation (SD)

The *p*-value indicates if any statistically significant difference was found between groups. Statistically significant *p*-values are in bold

*Mean (SD) based on 2009 US population norms

At evaluation of TSH and fT4 levels with quality of life, we found a direct and positive correlation between TSH level and physical role functioning ($r = 0.1968$, $p = 0.0144$) and emotional role functioning ($r = 0.1613$, $p = 0.0457$).

Cognitive function in Graves' disease patients according to thyroid hormone status

No significant difference was found in cognitive function, evaluated by MMSE, between patients in euthyroidism and hyperthyroidism (27.8 vs. 28.42, $p = 0.067$) as well as in subgroups ($p = 0.344$). We found a positive correlation between the free T4 level and the MMSE score ($r = 0.1645$, $p = 0.0415$). A shorter disease duration was a factor associated with better recall ($p < 0.0001$), attention and calculation ($p = 0.019$).

Table 4 36-Item Short Form Health Survey (SF-36) and Graves' Orbitopathy Quality of Life Questionnaire comparing patient's subgroups according to disease state

	Hypothyroidism after RIT	Hypothyroidism after thyroidectomy	Active disease with normal thyroid function	Active disease with hyperthyroidism	Disease remission	*p*-value
36-Item Short Form Healthy Survey (SF-36)						
Physical functioning*	90.43 ± 15.48	92.00 ± 10.93	92.41 ± 10.04	85.38 ± 21.91	95.87 ± 6.33	0.594
Physical role functioning*	**84.48 ± 35.61**	**85.00 ± 29.69**	**72.22 ± 44.04**	**59.62 ± 47.47**	**89.13 ± 29.99**	**0.028**
Bodily pain*	64.22 ± 27.74	77.60 ± 21.27	73.67 ± 24.53	72.12 ± 30.33	75.09 ± 26.40	0.246
General health perception*	71.57 ±26.08	74.80 ± 20.88	79.74 ± 17.91	66.31 ± 28.62	73.43 ± 26.98	0.508
Vitality*	70.43 ± 25.59	71.75 ± 15.58	74.81 ± 24.79	70.58 ± 27.14	79.57 ± 15.22	0.648
Social role functioning*	91.38 ± 20.31	86.25 ± 20.64	90.28 ± 18.13	94.17 ± 12.34	96.74 ± 10.80	0.259
Emotional role functioning*	85.06 ± 35.42	83.33 ± 35.05	72.84 ± 44.37	61.54 ± 47.79	88.40 ± 31.16	0.051
Mental health*	71.79 ± 26.07	69.80 ± 22.87	73.63 ± 28.53	69.23 ± 25.84	82.87 ± 18.89	0.421
Physical component scale*	50.01 ± 8.08	53.02 ± 6.23	52.01 ± 5.01	48.82 ± 9.76	52.35 ± 3.89	0.718
Mental component scale*	51.67 ± 11.80	49.44 ± 9.79	50.46 ± 13.18	49.01 ± 10.49	54.98 ± 8.45	0.301
Graves' Orbitopathy Quality of Life Questionnaire						
Visual function	95.71 ± 6.52	93.74 ± 7.79	95.23 ± 8.68	88.93 ± 9.27	97.62 ± 5.83	0.163
Appearance	67.08 ± 30.39	61.72 ± 26.80	72.92 ± 20.41	53.98 ± 25.81	72.92 ± 28.96	0.571

Values are expressed as mean and standard deviation (SD)

The *p*-value indicates if any statistically significant difference was found between groups. Statistically significant *p*-values are in bold

*Mean (SD) based on 2009 US population norms

Discussion

In this study, we found a poor quality of life at both subgroups with active Graves' disease, both in hyperthyroidism and euthyroidism patients using thionamides, particularly in physical and emotional scales. A better quality of life was associated with male sex, younger ages at diagnosis, normal thyroid function and absence of eye disease. No difference was found in cognitive evaluation; however, a shorter disease duration was associated with better memory, attention and calculation.

Our study is in agreement with others presented in literature [11–13], that similarly found a poor quality of life among patients with overt hyperthyroidism, probably due to the physical limitations imposed by the symptoms related to the disease, in association with psychiatric symptoms, also described by Chattopadhyay et al. [14]. in a case-control study in patients with a recent diagnosis of GD. They found significantly higher rates of psychiatric manifestations, including generalized anxiety and mood disorder compared to healthy control group. Some prospective studies also described a persistent impairment in quality of life even after months or years of euthyroidism [6, 7]. Cramon et al. [7]. found a severe disease-specific (evaluated by the thyroid-related patient-reported outcome—ThyPRO) and generic HRQoL (evaluated by SF-36) impairments in Graves' hyperthyroidism and toxic nodular goiter. The same HRQoL deficits were found in both groups after 6 months of treatment. Likewise, Abraham-Nording et al. [6]. found lower scores of vitality, even many years after treatment, when compared GD patients with a large Swedish reference group. At the same time, they did not find a difference in the quality of life scores among the three treatments modalities (antithyroid drugs, radioiodine, and surgery). In contrast, we found a difference between patients using thionamides, apart from thyroid status but still in activity of the autoimmune disease, and other groups of treatment, possibly because of higher levels of FT4 associated partial improvement of hyperthyroidism symptoms, stress and anxiety related to treatment. Male patients presented higher scores on quality of life, in pain and mental health, when compared to women. However, we did not find previous studies that mentioned this difference.

Not only HRQoL questionnaires showed a decrease in quality of life among GD patients, some authors had already evidenced brain changes in imaging tests during overt hyperthyroidism and its association with symptoms reported by patients [15, 16]. Schreckenberger et al. [15]. carried out a cross-sectional study in patients with untreated Graves' disease and healthy controls, correlating the level of anxiety and depression with findings on cerebral glucose metabolism assessed by PET fluorodeoxyglucose. Patients with hyperthyroidism had decreased glucose metabolism in the

limbic system, which was associated with the severity of anxiety and depression. Zhang et al. [16]. compared patients in hyperthyroidism and healthy controls with functional MRI, and found that patients with hyperthyroidism had poor connectivity between anterior cingulate cortex, posterior cingulate cortex, and left hippocampus, and between the right hippocampus and orbitofrontal right medial cortex, brain areas involved with emotional and cognitive control.

Only among patients with ophthalmopathy and hyperthyroidism at evaluation, a greater impairment of visual function was seen, but they did not show a difference in appearance or when they were divided into subgroups. In meantime, most patients reported that they used to avoid photographs and public places, and tried to hide proptosis using sunglasses and make-up. Many others studies, in different countries, showed a worsening quality of life in both visual function and appearance, especially when it is associated with a worse CAS score [8, 17]. Quality of life in GD patients with ophthalmopathy is also a public health concern since can affect psychosocial function, hobbies, and employment, with loss of productivity and increase in coasts at work [18]. Besides the concern about costs with the disease, a Danish study evaluated the incidence of suicide in GD patients and reported an increased suicide rate in GD overall, which is even higher in patients with ophthalmopathy [19].

No difference was found in cognitive function, by MMSE punctuation, between patients in euthyroidism or hyperthyroidism, as well as in their subgroups. However, a shorter disease duration was a factor associated with better recall, attention, and calculation. The MMSE is not the best tool to evaluate cognition in young patients since it is more commonly used in the evaluation of dementia in the elderly, however it is simple, objective and can be applied by any physician and it has been used for a long time. The studies are quite contradictory in relation to the association between hyperthyroidism, overt or subclinical, and cognition, probably because of population variation and the huge diversity of tests for cognition evaluation [20].

Samuels et al. [21, 22]. evaluated young women using suppressive therapy with LT4 and found no difference in cognition, nor when they evaluated older men with no thyroid disease, in relation to cognition and TSH and fT4 levels. Moon et al. [23]. also evaluated older patients with thyroid cancer using suppressive levothyroxine therapy and were compared with healthy controls, they did not find any cognitive impairment. Furthermore, they also describe positive correlations between serum T4 levels and some cognitive domains suggesting a potential beneficial effect of exogenous levothyroxine.

Other studies, from all over the world (Brazil, Italy, Korea), demonstrated the association between dementia and subclinical hyperthyroidism in older adults [24–26]. In contrast, Aubert et al. [27]. found a higher risk of dementia and a larger cognitive decline only among older adults with subclinical hyperthyroidism with a TSH < 0.10mIU/L. Not only TSH levels have been associated with dementia, one recent Australian study has already shown a link between higher fT4 levels and cognitive decline in older man [28].

As for Graves' disease patients, Vogel et al. [5]. compared 31 newly diagnosed patients and in thyrotoxicosis, with 34 healthy individuals. No difference between patients and the control group on neuropsychological tests were found. Lillevang-Johansen et al. [29]. evaluated discordant twin pairs and likewise Vogel et al. they did not demonstrate any clinically relevant negative impact of previous hyperthyroidism on long-term cognitive function.

As a limitation of the study, we can cite the small number of patients in each group and the lack of a prospective evaluation. However, the use of combined tools to assess the quality of life and cognitive function, applied at the same day and by the same physician, is considered as a strong point of our study.

In conclusion, we found a great impairment in quality of life among patients with active GD, especially in physical and emotional areas, even in those with normal thyroid function receiving thionamides. Ophthalmopathy was a factor associated with a poor quality of life and no clear evidence of cognitive impairment was demonstrated. These types of evidence stimulate a discussion about psychological and social well-being among patients with GD, presenting with eye disease or not, and if we are giving the proper attention for them or if we are just worried about TSH and fT4 levels. Physicians must concern about diagnosis and treatment, but they must also be aware of the importance of recognizing, as soon as possible, any sign of psychological suffering.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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RESEARCH LETTER

In children with acquired hypothyroidism levothyroxine requirements may be significantly conditioned by the etiology of thyroid failure

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Introduction

Hypothyroidism, either congenital or acquired (AH), is a common pediatric condition which needs a prolonged treatment with levo-thyroxine (L-T4), aiming to prevent growth and intellectual alterations. The goal of therapy is to restore patients' FT4 levels within reference range.

In hypothyroid patients L-T4 requirements are conditioned by residual thyroid function, body weight, age and adherence to treatment [1]. Another factor which can condition L-T4 requirements is the etiology of thyroid failure [2–6]. However, in pediatric age there are no consensus guidelines on the variations of L-T4 dosages according to the different causes of hypothyroidism [7].

In this study we retrospectively evaluated the adequacy of L-T4 doses in 54 young patients with AH, who were treated for at least three years. The patients were divided into two groups according to whether they were affected by either a Hashimoto's thyroiditis (HT) - related hypothyroidism or an AH of central origin (CeH).

Our aim was to ascertain whether L-T4 requirements are different in cases with different causes of AH.

Patients and methods

From a population of 302 patients <18 years with AH, who were followed in our center during the period 2008–2017, we enrolled only those who: (a) were old <15.0 years at diagnosis; (b) were old between 10.1 and 17.9 years at recruitment; (c) had received L-T4 therapy for at least 3 years before recruitment; (d) had undergone semestral titration of LT4 doses on the basis of clinical evaluation and thyroid test monitoring; (e) were clinically and biochemically euthyroid at 1, 2, and 3 years of therapy.

Exclusion criteria: (a) non-caucasian origin; (b) concomitant therapies with antiepileptic or iodinated drugs or glucocorticoids; (c) concomitant untreated celiac disease.

We selected 54 patients (31 girls), who were aged between 4.1 and 14.8 years at AH diagnosis (median 10.2 yrs) and between 10.1 and 17.9 years at recruitment (median 16.0 yrs) and were treated with L-T4 for 3–9 years (median treatment duration at recruitment 4.8 yrs).

Patients were divided into two groups according to the cause of AH: (a) 27 with CeH (13 girls; median age at diagnosis 9.0 years, range 4.1–14.7; median age at recruitment 15.8, range 10.1–17.9); (b) 27 with HT-related hypothyroidism (18 girls; median age at diagnosis 10.2 years, range 8.5–14.8; median age at recruitment 16.0 yrs, range 10.3–17.8).

In Group A patients, CeH was due to surgical treatment of pituitary tumors (craniopharyngiomas in 44.4% of cases, other supra-sellar tumors in 44.4% and functional adenomas in 11.2%). Six of them undergone also radiotherapy. In all cases CeH was associated with other hormone deficiencies, which required other hormonal subtstitution.

In Group B patients, diagnosis of HT was based on both thyroid ultrasonography characteristics and the positivity for serum thyroid peroxidase and/or thyroglobulin autoantibodies (TPOAbs and TGAbs) at titers above the upper limits of reference ranges.

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Data at AH diagnosis and during follow-up were recorded from patients' files.

Serum TSH (reference range 0.3–4.9 mIU/L), FT4 (reference range 10.3–24.4 pmol/L) and FT3 (reference range 2.0–4.4 pg/ml) were measured by radioimmunoassays, whilst anti-TPOAbs (reference range 0–20 IU/L) and anti-TGAbs (reference range 0–30 mIU/L) were measured by chemiluminescent immnunometric assays [8, 9].

In Group A diagnosis of hypothyroidism was based on clinical signs, which were associated with low FT4 and TSH levels low or in the normal range. In Group B diagnosis was based on clinical signs, which were associated with increased TSH and low or normal FT4 levels.

Full replacement L-T4 dosage in Group A was defined as the dose which yelded clinical euthyroidism and FT4 values in the upper half of reference range; in Group B it was defined as the dose required to normalize TSH concentrations [5].

Statistical analyses was based on non-parametric tests (Mann–Whitney and Spearman) and data are expressed as median and range.

A receiver operating characteristic (ROC) curve analysis was performed to identify the optimal cutoff values of L-T4 doses which were able to distinguish between the children with either CeH or HT-related hypothyroidism, at 1, 2, and 3 years of treatment. A $p < 0.05$ was considered significant.

Results

Both at diagnosis and at recruitment median patient ages in both groups were not different. In Group A, 13 out of 27 patients showed serum TSH values >0.5 mU/L (range 0.7–4.3). In Group B, 7 out of 27 patients demonstrated subclinical hypothyroidism.

Median L-T4 doses (mcg/kg/day) needed to maintain euthyroidism were higher in Group A than in Group B at 1 (2.1, range 1.1–5.7 vs 1.5, range 0.7–2.1; $p = 0.001$), 2 (2.3, range 1.4–4.6 vs 1.4, range 0.6–2.1; $p = 0.002$) and 3 years of treatment (1.7, range 0.6–2.9 vs 1.4, range 1.0–2.2; $p = 0.007$). The difference was still significant after the exclusion of patients with subclinical hypothyroidism in group B ($p = 0.002$, $p = 0.002$ and $p = 0.008$ at 1, 2 and 3 year of treatment respectively). The wide range of L-T4 doses in group A patients was due to the very high doses of L-T4 needed only in one case to achieve normalization of FT4 values. Nevertheless, when we recalculated median L-T4 doses after exclusion of this patient, the comparison between the two groups was still significant ($p = 0.003$ and $p = 0.005$ respectively at 1 and 2 year of treatment).

In both groups median FT4 levels were not significantly different at 1 (13.2 pmol/L, range 11.0–23.9. vs 16 pmol/L, range 11.0–22.0.; $p = 0.13$), 2 (14.5 pmol/L, range 10.4–22.0. vs 16.7 pmol/L, range 10.6–23.2; $p = 0.9$) and 3 years of treatment (13.6 pmol/L, range 10.9–23.3 vs 16.0 pmol/L, range 10.5–22.7; $p = 0.16$). During treatment, increased FT3 levels were not demonstrated in any patient (median 3.2 pg/ml, range 1.6–4.0; 3.4 pg/dl range 2.2–4.3; 3.4 pg/dl range 2.8–3.9 at 1, 2 and 3 year of treatment respectively), excluding L-T4 overtreatment. No relationships between L-T4 doses and FT4 levels were detected at any times.

The ROC curves are shown in Fig. 1. The optimal cutoff values between the two groups for each year are shown in the same figure. A specificity of 89–93% in the differential diagnosis between CeH and HT-related hypothyroidism was found at 1, 2 and 3 years of treatment. In addition p-value associated at AUC is significant in each year of treatment (in particular in 1st year $p < 0.0001$, in 2nd year $p = 0.002$ and 3rd year $p = 0.007$).

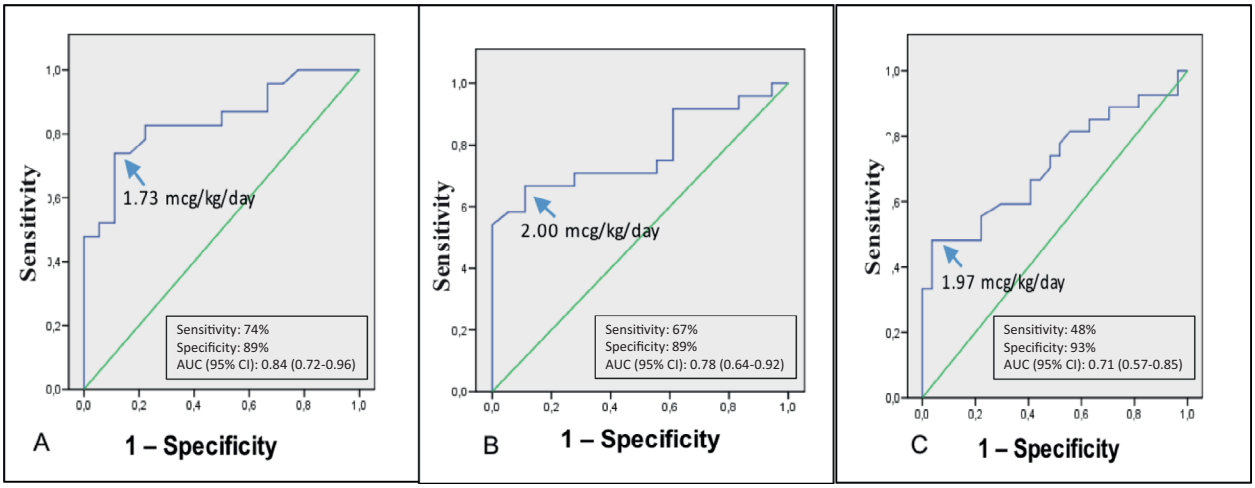

Fig. 1 Receiver Operating Characteristic (ROC) curve analysis applied to L-T4 doses at 1 **a**, 2 **b** and 3 **c** years of treatment; the best cutoff values and the area under curve (AUC) for each ROC curve are also provided

During the treatment period no side effects related to L-T4 administration were reported.

Discussion

L-T4 therapy is currently used for the management of both primary and secondary hypothyroidism, but its monitoring differs in these conditions. Whereas in primary hypothyroidism treatment is guided by normalizing TSH values, in CeH TSH levels may be low or normal and are, therefore, less helpful. Persani et al. demonstrated that CeH is due to impaired TSH bioactivity in many cases, explaining why low FT4 values can be associated to TSH levels in the normal range or slightly increased [3].

In CeH patients symptoms and FT4 concentrations are generally proposed as suitable monitoring tools [2]. It is discussed whether the L-T4 doses needed for correction of hypothyroidism are different in the patients with either CeH or primary hypothyroidism [2, 5, 10–14].

In this study we compared the adequacy of L-T4 doses in two cohorts of children with AH, who became hypothyroid at similar ages, as consequence of two different causes. This design gave us the opportunity of ascertaining whether L-T4 requirements differ in patients with either secondary or primary AH, irrespectively of age at the development of hypothyroidism.

We infer that the patients with CeH, when compared to those with HT-related hypothyroidism, need higher L-T4 doses to reach and maintain euthyroid state. It has to be considered that full replacement L-T4 dosage in the children with CeH was defined as the dose which yelded clinical euthyroidism and FT4 values in the upper half of the reference range, whereas in the individuals with HT-related hypothyroidism it was defined as the dose needed to normalize TSH levels. This can explain why achieving optimal L-T4 replacement is more difficult in AH patients with TSH deficiency than in those with HT-related hypothyroidism, due to the inability to be guided by TSH concentrations [2].

Another explanation for the higher L-T4 requirements recorded in CeH patients might be that the absence of thyroid stimulation can make these subjects functionally athyreotic and account for the higher L-T4 dosages [5]. In contrast, the patients with HT-related hypothyroidism cannot be considered athyreotic, especially in the cases with mild and restricted inflammation process. Such explanation is consistent with the view that L-T4 requirements in hypothyroidism are conditioned by residual mass of functioning thyroid tissue, as suggested by others [4].

To sum up, our data do not support the idea that L-T4 requirements are similar in patients with either CeH or primary hypothyroidism, as postulated by others [10, 11]. In contrast, according to our results, the L-T4 doses which are needed to maintain euthyroidism, are higher in children with CeH than in those with HT-related hypothyroidism. Furthermore, in this study the ROC curves were able to identify specific cut-off values among patients from these groups, which confirmed a clear discrimination, in terms of L-T4 requirements.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration.

Informed consent Informed parental consent for participation in the study was obtained for patients and the study was authorized by the Hospital Ethical Research Committee.

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ORIGINAL ARTICLE

Constant iodine intake through the diet could improve hypothyroidism treatment: a case report

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Abstract
Currently, hypothyroidism is usually treated only with drugs; patients are never told that they could regulate their levels of iodine with dietary recommendations in a complementary way. The objective of this work was to explore the effect of a constant iodine intake through the diet in a postmenopausal woman with subclinical grade II hypothyroidism, who also had mild hypercholesterolemia and obesity. Baseline anthropometric nutritional, pharmacological, and habit data were obtained, then the woman was scheduled for 1 month a diet in which she was provided food naturally containing iodine, so that the recommended requirements (iodine 150 μg/day) were met. All the information about which foods contain this mineral was supplied and explained to the patient. This diet was also designed to help her to gradually lose weight, and was more balanced and closer to the nutritional recommendations. The results obtained in this work were satisfactory, having achieved improved blood levels of thyroid-stimulating hormone (1.78 μIU/mL) and reduced total cholesterol levels (198 mg/dL). Statement of hypercholesterolemia was demoted. In addition, a significant improvement in relation to weight and body volume was reached (body mass index fell from 30.13 to 28.5 kg/m^2), an important fact since it has impacted the overall well-being of the patient. In conclusion, it was demonstrated that a constant iodine intake through the diet for this patient with grade II hypothyroidism was very effective, and therefore, this aspect should be also considered during hypothyroidism treatment.

Keywords Hypothyroidism · Iodine nutrition · Iodine food · Balanced diet · Case report

Abbreviations
TSH Thyroid-stimulating hormone

Introduction

Hypothyroidism is a state generated by an underactive thyroid gland which generally implies that all the metabolic processes of the individual are carried out more slowly; thus, symptoms like cold intolerance, constipation, fatigue, weight gain, dry skin, goiter, and even depression can also occur [1–3]. The thyroid gland synthesizes thyroid hormones, tetraiodothyronine or thyroxine (T4) and triiodothyronine (T3), from the amino acid tyrosine and the iodine ingested [3]. Hypothyroidism is usually treated only with drugs such as L-thyroxine (sodium levothyroxine) that externally provide the amount of iodine required for each patient. But, the natural sources of iodine for human beings are foods [3]. Patients are rarely told that they could improve or regulate their levels of iodine with dietary recommendations together with their medical treatment. Nobody tells them about which foods could be an aid in those specific situations in which it is known that thyroid hormone levels are altered (stress, traveling, etc.). Most of these patients are prone to get fat and/or to retain fluids due to their slowed metabolism; thus, a few doctors recommend some type of basic slimming diet, but nothing related to iodine intake through food, nor indeed any explanation of anything in this regard to the patient. The aim of the current study was to provide a balanced diet for 1 month which contained iodinate foods, appropriate for a person treated with sodium levothyroxine to evaluate its effect on the

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patient's welfare. In this case, we studied a postmenopausal woman with subclinical grade II hypothyroidism who also had mild hypercholesterolemia and obesity.

Patient case presentation

A 52-year-old woman with a profile of controlled euthyroid, with autoimmune hypothyroidism diagnosed 2 years ago, following a treatment of 75 mg/day sodium levothyroxine and 20 mg/day atorvastatin, was studied. The subject of the case was also diagnosed with the following pathologies: hypertension, dyslipidemia (hypertriglyceridemia, hypercholesterolemia), overweight, diabetes/intolerance to glucose, and cardiovascular diseases (angina pectoris, heart attack, and arrhythmia). She is not allergic to any medicine. This housewife is a smoker which has undergone two cesarean section surgical procedures and usually suffers from constipation. The subject also provided her medical analysis obtained through her family doctor. After obtaining the signed consent of the subject of the study, an anthropometric study was performed on her according to Norton and Olds [3]; a dietary history for 15 days, a food frequency questionnaire, and a 24-h recall questionnaire were also completed. The obtained values of the diets were calibrated using the "Manual Adjustment Diets" Excel program [5], and to obtain other nutritional standard indexes, formulas included in the DIAL Calculator program were used [6, 7]. The pharmacological vademecum [8] was consulted to determine drug/food interactions. This case report has been written based on Cohen recommendations [9].

Results and discussion

Sodium levothyroxine is the main drug used to treat hypothyroidism all around the world, although the doses that must be prescribed are not clear [10]. Patients are monitored throughout their life to adjust the amount of levothyroxine, usually every 6 months, but in special situations (stress, travel, social or personal challenges, etc.), these doses are insufficient and serum TSH levels increase. TSH is produced by the pituitary gland and its function consists of ordering the thyroid gland to produce and secrete thyroid hormones in the blood [1]; it is therefore the main medical control parameter for hypothyroid patients.

Foods are the natural source of iodine; thus, it seemed to be very interesting to evaluate the effect of a supervised diet that continuously provided the recommended iodine levels (150 μg/day) [6] in hypothyroid patients. A postmenopausal woman with subclinical grade II hypothyroidism was assayed. According to the data obtained, nutritional theoretical data were calculated as follows: basal metabolic rate (BMR) = 1202.6 kcal, resting energy expenditure rate at rest for older persons = 1279.6 kcal, and estimated total energy expenditure (TEE) = 1983.38 kcal, considering that the subject of the study performs "light work" [6, 11]. The usual food intake of the female object of this study was also achieved and media of the data obtained ($n = 15$ days) are shown in Table 1.

According to the data initially obtained, the patient was provided with a balanced but moderate slimming diet for 1 month, which contained food necessary to maintain levels of iodine intake of 150 μg/day. It contained foods belonging to all groups (animals, dairy products, vegetables, legumes, fruits, etc.) that every day provided iodine that could be used for the synthesis of thyroid hormones. The new planned diet also accomplished the recommended ratios for all food

Table 1 Comparison between mean data ($n = 30$) of macro- and micronutrients of the diet followed by the patient before this nutritional intervention and mean data corresponding to the proposed diet

	Before[a]	Proposed[a]	Recommendation (units)
Energy	1919	1463 [4]	1300–1500 kcal
Carbohydrates	38	54	50–55%
Protein	28	18	10–19%
Total protein	72.89	67	65.1–67 g
Animal/vegetable protein	4.48	0.95	Ratio = 1
Lipids	34	27	< 30%
MUFA	14.15	25	20–30 g
PUFA	5.92	8	7–8 g
SFA	12.35	7	10–11 g
Water	751.91	2646	1500–2500 mL
Calcium	508.88	983	800–1000 mg
Cholesterol	225.51	107	≤ 200 mg
Fiber	9.57	28	25–30 g
Phosphorus	924.03	1084	800 mg
Iron	7.31	14.23	10 mg
Magnesium	179.73	382	280 mg
Niacin	16.90	21.86	14 mg
Potassium	2130.59	4301	4700 mg
Sodium	1443.78	2672	≤ 3000 mg
Iodine (μg)	80	150	150 μg
Vitamin A	773.31	1286	800 μg
Vitamin B_1	0.86	1.24	1.1 mg
Vitamin B_{12}	3.97	4.89	2 μg
Vitamin B_2	1.03	1.34	1.4 mg
Vitamin B_6	1.55	2.53	1.5 mg
Vitamin C	110.66	237	60 mg
Vitamin D	3.04	3.3	5 μg
Vitamin E	5.27	15	8 mg
Folic acid	157.01	449	400 μg

MUFA monounsaturated fatty acids, *PUFA* polyunsaturated fatty acids, *SFA* saturated fatty acids

[a] The same units as recommendations

Table 2 Anthropometric data of the subject before and after the nutritional intervention

Anthropometric data (units)	Before the nutritional intervention	After the nutritional intervention
Weight (kg)	65.1	61.6
Height (m)	1.47	1.47
BMI (kg/m^2)	30.13	28.5
Wrist circumference (cm)	16	15.5
Waist circumference (cm)	86	84
Hip circumference (cm)	100	100
(Waist/hip girth ratio)	0.86	0.84
Arm circumference (cm)	24	22
Subscapular fold (mm)	14	14
Triceps fold (mm)	22	21
Bicipital fold (mm)	23	21
Abdominal fold (mm)	28	24

groups [12] (4–5 cereals/day, 3–4 vegetables/day, 3 fruits/day, 4 fish/week, 3 meat/week, 3 olive oil/day, etc.). The number of meals was regularized to five (% energy followed the recommendations [12]), and she was forced to take at least a first and second plate plus dessert at the midday meal. Regarding food, excessive consumption of cruciferous vegetables and rich foods high in cholesterol was moderated (cheese, whole milk, "Greek" type yoghurt), and consumption of fish, fruit and vegetables and olive oil was increased. Mean data after the nutritional intervention were collected, studied, and compared with European recommendations [12]. The results in Table 1 show that the recommendations for macro- and micronutrients were reached when the subject followed the diet proposed in the nutritional intervention.

Anthropometric data of the subject of this work were compared before and after the 1-month diet (Table 2). The subject presented a BMI (body mass index) of 30.13 kg/m^2 related to obesity type I [6] and an WHR (waist-hip ratio) of 0.86 which was also an indicator of obesity since it is above the normal values stated for women of between 0.71 and 0.84 [12].

Biochemistry data of the subject studied were provided by her medical specialist, before and after the nutritional intervention (Table 3).

The biochemistry data obtained after this nutritional intervention demonstrated substantial improvement in the level of TSH which reduced from 11.12 μIU/mL (that surpassed suitable values) to 1.78 μIU/mL. This low level relaxes the irregular and continued demand on the thyroid gland. According to these results, it appears that regularization of the consumption of foods with an adequate amount of iodine is a valuable aid for these patients. The objective of recommending this type of diet for hypothyroid people is not to contribute to an iodine excess but to help regulate medication doses by means of natural sources of this micronutrient [13, 14]. To the best of our knowledge, in the scientific literature consulted, there is no research indicating that a diet covering the iodine recommendations should be counter-productive in patients who take sodium levothyroxine. Only hyperthyroidic

Table 3 Biochemistry of the subject before and after the nutritional intervention

Thyroid				
Parameters	Before study	After nutritional intervention		Normal values
Thyrotropin (TSH)	11.12	1.78	μIU/mL	[0.34–5.6]
Free thyroxine (T4L)	0.79		ng/dL	[0.6–1.64]
Free triiodothyronine (T3L)	3.4		pg/mL	[2.5–3.9]
Thyroid peroxidase (ATPO)	756.90		IU/mL	[0.0–9.0]
Thyroid function profile		Probable subclinical hypothyroidism		
Lipid metabolism				
Parameters	Before study	After nutritional intervention		Normal values
Triglyceride	138	72	mg/dL	[50.0–190.0]
Total cholesterol	244	198	mg/dL	[140.0–200.0]
HDL cholesterol	62	48	mg/dL	[45.0–90.0]
Total cholesterol/HDL ratio	3.9	4.1	mg/dL	[2.5–4.5]
LDL cholesterol	154	136	mg/dL	[60.0–155.0]
	Ischemic heart disease	Normolipemic		
	Low risk of ischemic heart disease			< 100 mg/dL
	Moderate risk of ischemic heart disease			100–160 mg/dL
	High risk of ischemic heart disease			> 160 mg/dL
VLDL cholesterol	28	14	mg/dL	[5.0–40.0]

Data was provided by the medical specialist of the patient before and after the nutritional intervention; only data related to this study are shown

people with chronic Hashimoto disease must not take iodine because it aggravates that process; however, that is not the general case [14].

Neither the American nor European Thyroid Associations give any recommendation regarding any type of specific diet for these patients. The British Thyroid Association declared that if sodium levothyroxine is consumed, it is not necessary to take iodine supplements [13], although there is nothing against consuming the levels recommended in the diet. For this reason, in this work, a diet that did not contain excess iodine was well designed. At the same time, the subject of this study was also provided with basic nutritional education and related tables which included "adequate iodine content foods" and "less desirable foods" for cases of hypothyroidism, so when the nutritional intervention was finished, the subject had the necessary information available for her own regulation. It is not common for doctors to provide this type of information to their hypothyroid patients. This information was considered necessary as the patient of this study was a habitual consumer of cruciferous vegetables. Most scientific articles reveal that cruciferous vegetables clearly interfere with iodine bioavailability [14]. Understanding of the information provided was secured with simple questions. It was noted that her first impression was very favorable, and all this knowledge aroused great interest in this patient. The main objective of this diet was to ensure that an adequate level of dietetic iodine intake was maintained, but the occasion offered the opportunity to give a few fewer calories than this individual needed. Foods containing iodine can be found in all food groups, so it can be worked perfectly well into a balanced diet. It has been observed that a balanced diet helps a person to balance their own body to reach a suitable weight, so it is noteworthy that the weight of the patient in this case decreased 3.5 kg/month, so the BMI went from 30.13 to 28.5 kg/m^2 which meant that the patient went from the state of obesity that of being overweight [6]. WHR also dropped from 0.86 to 0.84, another good figure considering the recommendations [6]. In terms of lipid data, there was amelioration in the values for triglycerides which dropped to 138.72 mg/dL, total cholesterol which decreased from 244 to 198 mg/dL, and LDL cholesterol which decreased from 154 to 136 mg/dL, meaning a clear reduction in the risk of ischemic heart disease and improvement of health status in general. The consumption of a higher quantity of fruit and vegetables (fresh and dry although with iodine, i.e., strawberries, pears, pineapple, spinach, garlic, beans) meant recommended levels (25–30 g) were reached, which solved the problems with constipation. The contributions to the diet of minerals and vitamins such as calcium (very important for avoiding potential problems of osteoporosis in postmenopausal women, always accompanied with appropriate levels of vitamin D), iron (fundamental to women and older individuals), magnesium (a factor for prevention of diabetes type II and important for the cardiovascular system), potassium (involved in the repair and generation of muscle mass), vitamins C, A, D, E, B_1, B_2, and folic acid also approached recommended levels since they are involved in converting hormone T4 into T3 [6]. In conclusion, a constant iodine intake, within the recommendations, through a balanced diet for patients with grade II hypothyroidism could be a very effective implement to improve the level of serum thyrotropin (TSH) along with medical treatments; therefore, this aspect should be considered.

Conclusion

The results obtained in this work have been satisfactory: the continued intake of iodine, following the recommendations, is sufficient to reach the level of thyrotropin within the normal values in blood. New biochemical data indicate that the patient no longer presents hypercholesterolemia and a significant improvement was observed in anthropometric results. Thus, it has been demonstrated that the combination of pharmacological treatment and a diet controlled by a nutritionist has been very effective for this patient with hypothyroidism. Therefore, dietary iodine should be also considered during hypothyroidism treatment.

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Compliance with ethical standards After obtaining the signed consent of the subject of the study, an anthropometric study was performed on her according to Norton and Olds [3]; a dietary history for 15 days, a food frequency questionnaire, and a 24-h recall questionnaire were also completed.

Conflict of interest The authors declare that they have no conflict of interest.

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