Prevalence of Growth Hormone Deficiency in Hashimoto’s Thyroiditis

Silvia A. Eskes, Erik Endert, Eric Fliers, and Wilmar M. Wiersinga

Department of Endocrinology and Metabolism, Academic Medical Center, University of Amsterdam, 1100 DD Amsterdam, The Netherlands

Context: Autoimmune hypophysitis can result in GH deficiency (GHD) and is associated with other autoimmune endocrine diseases like Hashimoto’s thyroiditis. Recent studies suggest a high prevalence (5%) of GHD in Hashimoto’s thyroiditis.

Objective: Our objective was to establish the prevalence of GHD in patients with treated autoimmune hypothyroidism (AIH).

Patients: We included patients with spontaneous AIH [thyroid peroxidase antibodies (TPO-Ab) ≥ 100 kU/liter], who were adequately treated with T4 (TSH 0.2–5.0 mU/liter). Exclusion criteria were previous 131I treatment, thyroid surgery, or a history of hypothalamic or pituitary disease. Patients were recruited via our outpatient clinics and via patient self-help organizations.

Design: We measured serum TSH, free T4, TPO-Ab, and IGF-I. If the IGF-I concentration was below the 10th percentile of age-specific reference values, a GHRH/GH-releasing peptide (GHRP)-6 test was done. GHD was defined as a GH peak after GHRH/GHRP-6 below the 2.5th percentile of age-specific reference values.

Main Outcome Measures: IGF-I concentration and GH peak after GHRH/GHRP-6 test were measured.

Results: From 860 patients who applied, 322 did not satisfy inclusion criteria (157 because TPO-Ab was < 100 kU/liter, 165 because TSH was < 0.2 or > 5.0 mU/liter), and 23 had an exclusion criterion. In the remaining study population of 515 patients (476 female, 39 male), 49 patients (9.5%) had an IGF-I concentration below the 10th percentile. These patients underwent a GHRH/GHRP-6 test. Two patients had a GH peak below the 2.5th percentile.

Conclusion: The prevalence of GHD in Dutch patients with AIH is 0.4% (two of 515).

GH deficiency (GHD) can be caused by a variety of conditions. Most adult patients have a history of hypothalamic-pituitary disease, such as a pituitary tumor, pituitary surgery or irradiation, head trauma, vascular injury, or infiltrative disease of the hypothalamus-pituitary region. In some cases, the cause of GHD is unknown. An uncommon cause is autoimmune (lymphocytic) hypophysitis. Autoimmune hypophysitis is frequently associated with other endocrine or nonendocrine autoimmune diseases.

Autoimmune hypophysitis can cause partial or total hypopituitarism, due to loss of selective adenohypophyseal cells or to more diffuse pituitary damage. Isolated or combined deficiencies of GH, L/H/FSH, ACTH, and TSH deficiency have been described so far (1–3). Two studies have suggested that isolated GH deficiency (GHD), as a result of autoimmune hypophysitis, may not be that uncommon, especially in patients with autoimmune thyroid disease (4, 5). Both studies evaluated pituitary function in Hashimoto’s thyroiditis patients and found isolated GHD in 5% (four of 80 and 32 of 707, respectively).

This may indicate that the prevalence of autoimmune GHD in patients with Hashimoto’s thyroiditis is much

Abbreviations: APA, Antipituitary antibodies; FT4, free T4; GHD, GH deficiency; GHRP, GH-releasing peptide; ITT, insulin tolerance test; TPO-Ab, thyroid peroxidase antibody titer.
higher than considered so far. Hashimoto’s thyroiditis is common, especially in women. Some hypothyroid patients who have been rendered euthyroid by adequate doses of T4, report a reduced quality of life (6, 7). It is tempting to speculate that this is caused by unrecognized GHD and that GH replacement would increase well-being in these patients. The aim of this study was to investigate the prevalence of GHD in patients with Hashimoto’s thyroiditis.

Patients and Methods

Patients

Patients were recruited from our outpatient clinics and via websites and information bulletins of patient self-help organizations (Schilddriekiektzichting Nederland, Dutch Society of Graves’ Disease Patients, and Hypo But Not Happy). Inclusion criteria were age from 20–70 yr, Hashimoto’s thyroiditis defined, besides an elevated TSH, as thyroid peroxidase antibody titer (TPO-Ab) ≥100 kU/liter (at present or ever documented in the past), and adequate T4 treatment (defined as serum TSH values from 0.2–5.0 mU/liter). Exclusion criteria were a history of hypothyroidic or pituitary disease, hypothyroidism after thyroid surgery or I131, pregnancy, or use of medications known to interfere with the GH-IGF-I axis (e.g. pharmacological doses of corticosteroids). Informed consent was obtained from all subjects, and the hospital’s ethical committee approved the study. The trial was registered (ISRCTN57632130).

Study protocol

Blood samples were drawn in the outpatient clinics for assessment of TSH, free T4 (FT4), TPO-Ab, and IGF-I concentration. In patients with IGF-I levels below the 10th percentile according to age-specific reference values (8), a GHRH/GH-releasing peptide (GHRP)-6 test was performed. Basal blood samples were taken at –30, –15, and 0 min. Then GHRH (Ferring GmbH, Kiel, Germany) and GHRP-6 (CLINALFA AG, Läufelfingen, Switzerland) were given as an iv bolus injection of 1 g GHRH/kg body weight and of 1 μg GHRP-6/kg body weight. Further samples were taken at 15, 30, 45, 60, 90, and 120 min. GH was measured in all samples. GHD was defined as a GH peak after GHRH/GHRP-6 below the 2.5th percentile of the age-specific reference values as established earlier in our clinic (8). When GHG was diagnosed, an insulin tolerance test (ITT) was done. Blood samples were taken at –15 and 0 min for measuring GH. After the blood sample at 0 min, 0.15 U/kg insulin (Actrapid; Novo Nordisk, Mainz, Germany) was iv administered. Additional blood samples for measuring GH were taken at 15, 30, 45, 60, and 75 min. The response was considered impaired if the GH peak was below the 2.5th percentile of age-specific reference values (8).

Analytical methods

FT4 and TSH were measured by time-resolved fluorimunoassay (Delfia FT4, Delfia hTSH Ultra, respectively; Wallac Oy, Turku, Finland). TSH intraassay variation was 1–2% and interassay variation 3–4%; detection limit was 0.01 mU/liter and reference range 0.4–4.0 mU/liter. FT4 intraassay variation was 4–6% and interassay variation 5–8%; detection limit was 2 pmol/liter and reference range 10–23 pmol/liter. TPO-Ab were determined by chemiluminescence immunoassay (LUMI-test antti-TPO; BRAHMS, Berlin, Germany) with intraassay variation of 3–7%, interassay variation of 8–12%, detection limit of 30 kU/liter, and reference value of less than 60 kU/liter. GH was determined by time-resolved fluorimunoassay (Delfia, PerkinElmer, Turku, Finland) with a detection limit of 0.1 mU/liter, an intraassay coefficient of variation of 6.4% at 3.4 mU/liter and 1.8% at 20.1 mU/liter, and an interassay coefficient of variation of 10.9% at 3.0 mU/liter and 7.7% at 21.7 mU/liter. Conversion factor for GH is 1 μg/liter = 3.67 mU/liter. IGF-I was measured on an Immulite 2000 system (Diagnostic Products Corp., Los Angeles, CA) with a detection limit of 5 nmol/liter, an intraassay coefficient of variation of 2.5% at 9.9 nmol/liter and 2.0% at 89 nmol/liter, and an interassay coefficient of variation of 5.2% at 10.6 nmol/liter and 4.1% at 55.8 nmol/liter.

Results

A total of 860 patients responded, of whom 322 could not be included in the study because of absence of an inclusion criterion [157 had TPO-Ab <100 kU/liter, 139 had oversupplementation with T4 (TSH <0.2 mU/liter) and 26 were undersupplemented (TSH >5.0 mU/liter). Furthermore, 23 patients were excluded because of a history of hypothyalmic or pituitary disease (four), hypothyroidism after thyroid surgery or I131 (13), pregnancy (two), use of interfering medications (one), or withdrawal from the study (three).

A total of 515 patients were included in the study (476 women and 39 men, mean age 47.4 ± 10.2 yr). They were euthyroid with T4 treatment (median TSH 1.1 mU/liter, range 0.2–5.0 mU/liter; median FT4 17.1 pmol/liter, range 7.6–38.2 pmol/liter), and median TPO-Ab was 1170 kU/liter (range 100 to 7000). Additionally, 23 patients were excluded because of a history of hypothyalmic or pituitary disease (four), hypothyroidism after thyroid surgery or I131 (13), pregnancy (two), use of interfering medications (one), or withdrawal from the study (three).

IGF-I was below the 10th percentile in 49 of 515 subjects (9.5%) (Fig. 1). Four of the 49 patients (8.2%) had associated autoimmune diseases, compared with 29 of 466 (6.2%) in subjects with IGF-I above the 10th percentile. Oral contraceptives were used by 15 of the 44 women (34%) in the group with IGF-I below the 10th percentile and by 41 of 432 (9.5%) in the group with IGF-I above the 10th percentile. Body mass index was 25.5 (range 16.0–46.0) and 25.8 (range 14.8–63.3) kg/m2 in subjects with an IGF-I value below the 10th percentile and by 41 of 432 (9.5%) in the group with IGF-I above the 10th percentile. Oral contraceptives were used by 15 of the 44 women (34%) in the group with IGF-I below the 10th percentile and by 41 of 432 (9.5%) in the group with IGF-I above the 10th percentile. Body mass index was 25.5 (range 16.0–46.0) and 25.8 (range 14.8–63.3) kg/m2 in subjects with an IGF-I value below the 10th percentile and at or above the 10th percentile, respectively.

The GHRH/GHRP-6 test was done in the 49 patients with IGF-I below the 10th percentile. Two of them had a GH peak below the 2.5th percentile. In one patient (male, 49 yr) the basal GH concentration was undetectable and did not rise after GHRH/GHRP-6. We performed an additional ITT, during which the GH concentration remained undetectable. This patient had no antipituitary
antibodies (APA), no other pituitary deficiencies, and a normal magnetic resonance imaging of the pituitary gland. In the other patient (female, 41 yr), the GH peak during the GHRH/GHRP-6 test was 24.5 mU/liter (age-specific cutoff value is 25.2 mU/liter), whereas the GH peak during the ITT was 16.6 mU/liter (age-specific cutoff value is 12.5 mU/liter). APA were absent, and the patient might have partial GHD or even no GHD at all. The other 47 patients had a mean GH peak of 130.8 ± 84.4 mU/liter (Fig. 2).

Consequently, in this Dutch group of treated Hashimoto’s thyroiditis patients, the prevalence of GHD tested with a GHRH/GHRP-6 test is 0.4% (two of 515).

**Discussion**

In our study, we found a low prevalence of GHD of 0.4% in patients with Hashimoto’s thyroiditis (or 0.2% if the
second GHD patient is disregarded in view of her almost normal responses). This is 10-fold lower than the prevalence of about 5% reported by others (4, 5). What could be the reason for this marked discrepancy?

Could it be patient selection? Our patient population is not a random selection, because we included patients who responded to advertisements on the websites and in the information bulletins of patient self-help organizations. This presumably led to a biased patient selection. Patients who are less satisfied with their health status and who have more complaints than the average patient will be more inclined to participate. However, that would elicit in all likelihood an overestimation of the prevalence of GHD. Furthermore, it seems not inappropriate to establish the presence of GHD in patients with complaints, because these are the patients who might potentially benefit from GH supplementation.

In the previous studies (4, 5), patients were selected for further investigation on the basis of the presence of APA. Patients with GHD in the Italian studies had significantly lower IGF-I concentrations than the patients without GHD (4, 5). We selected patients based on IGF-I because the sensitivity of the APA assay for GH is insufficient. IGF-I is a reliable marker for the severity of GHD (9), and all adult GHD patients have an IGF-I SD score of −1.50 or less (10).

Therefore, we think it is unlikely that we have missed patients with GHD by limiting further investigation to patients with IGF-I concentrations below the 10th percentile.

Could it be the methods used for diagnosing GHD? De Bellis et al. (4) used an ITT and an arginine test, whereas Manetti et al. (5) used a GHRH/arginine test for diagnosing GHD. We performed a GHRH/GHRP-6 test. Although the ITT is recommended as the gold standard test, the GHRH/GHRP-6 test is as sensitive and specific as the ITT for the diagnosis of adult GHD due to pituitary disease and has very few side effects (11, 12).

Could it be medication? All our patients were on L-T4 medication, which was not always the case in one of the previous studies (5). APA (the selection criterion for further testing in that study) was, however, not associated with thyroid status or with TPO-Ab. In our study, 56 subjects used oral contraceptives, which are known to lower the IGF-I concentration (13). It could have led to a higher proportion of patients with IGF-I values below the 10th percentile. This, however, was not the case in our study because 9.5% of our population had IGF-I values below the 10th percentile. The reasons for the obvious discrepancy between our results and those of the two previous Italian studies thus remain unclear.

In conclusion, we find a very low prevalence of GHD in patients with Hashimoto’s thyroiditis. Based on our study, it seems there is no place for routine tests of GH status in these patients.

Acknowledgments

We thank M. van Vessem-Timmermans and J. C. Langhout-Kors for assistance with performing the tests and M. J. Geerlings and E. M. Brian-Johannesma for assistance on laboratory analyses. We also thank Dr. R. B. Geskus, Ph.D., department of Clinical Epidemiology, Biostatistics, and Bioinformatics, for his help with making Figs. 1 and 2.

Address all correspondence and requests for reprints to: S. A. Eskes, Academic Medical Center Amsterdam, Department of Endocrinology and Metabolism, Meibergdreef 9, 1100 DD Amsterdam, The Netherlands. E-mail: s.a.eskes@amc.uva.nl.

This study was funded by Ipsen Pharmaceuticals, Hoofddorp, The Netherlands. The study sponsor had no participation in study design, data collection, analysis, interpretation, or manuscript writing.

Disclosure Summary: The authors have nothing else to disclose.

References

the growth hormone status in young adults with childhood-onset
growth hormone deficiency: reappraisal of insulin tolerance testing.
J Clin Endocrinol Metab 94:4195–4204
G, Lombardi G 2009 A reappraisal of diagnosing GH deficiency in
adults: Role of gender, age, waist circumference, and body mass
index. J Clin Endocrinol Metab 94:4414–4422
11. Popovic V, Leal A, Micic D, Koppeschaar HP, Torres E, Paramo C,
Obradovic S, Dieguez C, Casanueva FF 2000 GH-releasing hor-
mone and GH-releasing peptide-6 for diagnostic testing in GH-de-
deficiency in adults by testing with GHRP-6 alone or in combination
with GHRH: comparison with the insulin tolerance test. Eur J En-
docrinol 146:667–672
13. Juul A 2003 Serum levels of insulin-like growth factor I and its
binding proteins in health and disease. Growth Horm IGF-I Res
13:113–170