Clinical studies on thyroid diseases
Eskes, Silvia

Citation for published version (APA):
Eskes, S. A. (2014). Clinical studies on thyroid diseases

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 3b

Prevalence of growth hormone deficiency in Hashimoto’s thyroiditis.

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

Journal of Clinical Endocrinology and Metabolism 2010; 95(5): 2266-2270
ABSTRACT

Context: Autoimmune hypophysitis can result in growth hormone 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: To establish the prevalence of growth hormone deficiency in patients with treated autoimmune hypothyroidism (AIH).

Patients: We included patients with spontaneous AIH (TPO-Ab ≥ 100 kU/L), who were adequately treated with thyroxine (TSH 0.2 – 5.0 mU/L). Exclusion criteria were prior I131 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, FT4, TPO-Ab and IGF-I. If the IGF-I concentration was < 10th percentile of age specific reference values, a GHRH/GHRP-6 test was done. GHD was defined as a growth hormone peak after GHRH/GHRP-6 < 2.5th percentile of age specific reference values.

Main outcome measures: IGF-I concentration and GH peak after GHRH/GHRP-6 test.

Results: From 860 patients who applied, 322 did not satisfy inclusion criteria (157 because TPO-Ab < 100 kU/L, 165 because TSH < 0.2 or > 5.0 mU/L) 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 < 10th percentile. These patients underwent a GHRH/GHRP-6 test. Two patients had a growth hormone peak < 2.5th percentile.

Conclusion: The prevalence of GHD in Dutch patients with AIH is 0.4% (2 out of 515).
INTRODUCTION

Growth hormone deficiency (GHD) can be caused by a variety of conditions. Most adult patients have a history of hypothalamic-pituitary disease, such as a pituitary tumour, 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 non-endocrine 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 growth hormone (GH), LH/FSH, ACTH and TSH deficiency have been described so far. Two studies have suggested that isolated GHD, as a result of autoimmune hypophysitis, may not be that uncommon, especially in patients with autoimmune thyroid disease (AITD). Both studies evaluated pituitary function in Hashimoto’s thyroiditis patients and found isolated GHD in 5% (4/80 and 32/707 respectively). This may indicate that the prevalence of autoimmune GHD in patients with Hashimoto’s thyroiditis is much 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 thyroxine, report a reduced quality of life. It is tempting to speculate that this is caused by unrecognized GHD and that growth hormone replacement would increase wellbeing in these patients. The aim of this study was to investigate the prevalence of GHD in patients with Hashimoto’s thyroiditis.

PATIENTS AND METHODS

Subjects
Patients were recruited from our outpatient clinics and via websites and information bulletins of patient self-help organizations (‘Schildklierstichting Nederland’, Dutch Society of Graves’ Disease Patients and ‘Hypo but not Happy’). Inclusion criteria were age between 20-70 years, Hashimoto’s thyroiditis (defined –besides an elevated TSH- as TPO antibody titer ≥ 100 kU/l (at present or ever documented in the past), and adequate thyroxine treatment (defined as serum TSH values between 0.2-5.0 mU/l). Exclusion criteria were a history of hypothalamic 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 registrated (ISRCTN57632130).

Study protocol
Blood samples were drawn in the outpatient clinics for assessment of TSH, FT₄, TPO-Ab and IGF-1 concentration. In patients with IGF-I levels below the 10th percentile according to age specific reference values, a GHRH/GHRP-6 test was performed. Basal blood samples were taken at -30, -15 and 0 min. Then GHRH (Ferring GmbH, Kiel, Duitsland) and GHRP-6 (CLINALFA AG, Läufelfingen, Zwitserland) were given as an intravenous bolus injection of 1 μg GHRH/kg body weight and of 1 μg GHRP-6/ kg body weight. Further samples were taken at 15, 30, 45, 60, 90 en 120 min. Growth hormone (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. When GHD was diagnosed, an insulin
tolerance test (ITT) was done. Blood samples were taken at \( t = -15 \text{ min} \) and \( t = 0 \text{ min} \) for measuring GH. After the blood sample at \( t = 0 \text{ min} \), 0.15 U/kg Insulin (Actrapid Novo Nordisk, Mainz, Germany) was intravenously administered. Additional blood samples for measuring GH were taken at \( t = 15, 30, 45, 60 \) and 75 min. The response was considered impaired if the GH peak was below the 2.5\(^{th}\) percentile of age specific reference values \(^8\).

### Analytical methods

\( FT_4 \) and TSH were measured by time-resolved fluoroimmunoassay (Delfia FT4 and Delfia hTSH Ultra respectively, Wallac Oy, Turku, Finland). TSH: intra-assay variation: 1-2\%; inter-assay variation 3-4\%; detection limit 0.01 mU/l; reference range 0.4-4.0 mU/l. \( FT_4 \): intra-assay variation 4-6\%; inter-assay variation 5-8\%; detection limit 2 pmol/l; reference range 10-23 pmol/l. TPO-Ab were determined by chemiluminescence immunoassay (LUMI-test anti-TPO, BRAHMS, Berlin, Germany), intra-assay variation 3-7\%; inter-assay variation 8-12\%; detection limit 30 kU/l; reference value < 60 kU/l. GH was determined by time-resolved fluoroimmunoassay (Delfia, PerkinElmer, Turku, Finland) with a detection limit of 0.1 mU/l, an intra-assay coefficient of variation of 6.4\% at 3.4 mU/l and 1.8\% at 20.1 mU/l, and an interassay coefficient of variation of 10.9\% at 3.0 mU/l and 7.7\% at 21.7 mU/l. Conversion factor GH: 1 \( \mu g/l = 3.67 \) mU/l. IGF-1 was measured on an Immulite 2000 system (DPC, Los Angeles, USA) with a detection limit of 5 nmol/l, an intra-assay coefficient of variation of 2.5\% at 9.9 nmol/l and 2.0\% at 89 nmol/l, and an interassay coefficient of variation of 5.2\% at 10.6 nmol/l and 4.1\% at 55.8 nmol/l.

### RESULTS

860 patients responded, of whom 322 could not be included in the study because of absence of an inclusion criterium (157 had TPO antibodies < 100 kU/l, 139 had oversuppletion with thyroxine (TSH < 0.2 mU/l) and 26 were undersuppleted (TSH > 5.0 mU/l). Furthermore, 23 patients were excluded because of a history of hypothalamic or pituitary disease (4), hypothyroidism after thyroid surgery or \( ^{131}\text{T} \) (13), pregnancy (2), use of interfering medications (1) or withdrawal from the study (3).

A total of 515 patients were included in the study (476 women, 39 men, mean age 47.4 ± 10.2 years).

They were euthyroid with thyroxine treatment (median TSH 1.1 mU/l; range 0.2-5.0, \( FT_4 \) 17.1 pmol/l; 7.6-38.2), median TPO-Ab 1170 kU/l; range 100- >3000). Additional autoimmune diseases were pernicious anemia (n=18), vitiligo (n=7), type 1 DM (n=4), Addison’s disease (n=4) and premature ovarian failure (n=2). 56 women used oral contraconcepts.

IGF-I was < 10\(^{th}\) percentile of age specific reference values in 49/515 (9.5\%) subjects (figure 1). Four of the 49 patients (8.2\%) had associated autoimmune diseases, as compared to 29 out of 466 (6.2\%) in subjects with IGF-1 ≥ 10\(^{th}\) percentile. Oral contraceptives were used by 15 of the 44 women (34\%) in the group with IGF-1 < P10, and by 41 out of 432 (9.5\%) in the group with IGF-1 ≥P10. Body mass index was 25.5 (range 16.0-46.0) and 25.8 (range 14.8-63.3) in subjects with an IGF-1 value below P10 and ≥P10 respectively.

The GHRH/GHRP-6 test was done in the 49 patients with IGF-1 < P10.Two of them had a GH peak < 2.5\(^{th}\) percentile. In one patient (male, 49 yrs) the basal GH concentration was undetectable and did not rise after GHRH/GHRP-6. We performed an additional insulin tolerance test (ITT), during which the GH concentration remained undetectable. This patient had no APA.
no other pituitary deficiencies and a normal MRI of the pituitary gland. In the other patient (female, 41 yrs) the GH peak during the GHRH/GHRP-6 test was 24.5 mU/l (age specific cut off value: 25.2 mU/l), while the GH peak during the ITT was 16.6 mU/l (age specific cut off value: 12.5 mU/l). 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/l (figure 2). Consequently, in this Dutch group of treated Hashimoto’s thyroiditis patients, the prevalence of growth hormone deficiency tested with a GHRH/GHRP-6 test is 0.4% (2/515).
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 others4,5. 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 reacted on 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 suppletion.

In the previous studies4,5 patients were selected for further investigation on the basis of the presence of antipituitary antibodies (APA). Patients with GHD in the Italian studies had significantly lower IGF-I concentrations than the patients without GHD4,5. We selected patients based on IGF-I because the sensitivity of the APA assay for GHD is insufficient. IGF-I is a reliable marker for the severity of GHD9, and all adult GHD patients have an IGF-I SD score -1.50 or less10.

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 al4 used an insulin tolerance test (ITT) and an arginine test while Manetti et al5 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 diseases and has very few side effects11,12.

Could it be medication? All our patients were on L-thyroxine medication, which was not always the case in one of the previous studies5. 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 anticonceptives, which are known to lower the IGF-I concentration13. It could have led to a higher proportion of patients with IGF-I values < 10th percentile. This, however, was not the case in our study as 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 PhD, department of Clinical Epidemiology, Biostatistics and Bioinformatics, for his help with making figure 1 and 2.
This study was funded by Ipsen pharmaceuticals, the Netherlands. The study sponsor had no participation in study design, data collection, analysis, interpretation or manuscript writing.
REFERENCE LIST


