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LETTERS TO THE EDITOR

Treatment of Hemangiopericytoma-Induced Hypoglycemia with Growth Hormone and Corticosteroids[a]

To the editor:

A 56-yr-old man was admitted to our department because of recurrent and severe hypoglycemia. Ten years previously the patient had undergone surgery for an intraabdominal hemangiopericytoma, a mesenchymal tumor. An ileocolectomy with colostomy was performed about twenty months later because of local recurrence of the tumor. He was apparently well thereafter until 2 years before the admission to our department, when he was treated with chemotherapy and radiotherapy because of a small mass in the pelvis evidenced at a computed tomography scan. Two months before admission to our department, he was brought to the emergency room in a state of unconsciousness and with a plasma glucose level of 20 mg/dL (1.1 mM). He was given 20% dextrose iv, and he promptly recovered. The hypoglycemic episodes recurred and became more frequent. Upon admission to our department the patient was first treated with 50% dextrose infusion through a subclavian vein. Nevertheless episodes of hypoglycemia persisted, especially at night, when fasting was longer than 4–5 hr. Increased meal frequency with complex carbohydrates administration plus continuous dextrose infusion were no longer able to control hypoglycemia. The patient had normal-to-low plasma insulin levels and very high levels of insulin-like growth factor (IGF)-II, especially in the isoform 10–17 kDa, around 80% of total measured IGF-II (Fig. 1 and Table 1). The diagnosis of nonislet cell tumor hypoglycemia (NICTH) was proposed. Evaluation of liver showed metastatic lesions, but because of the size, a palliative surgical attempt was not advised. Therapy with both prednisone (15 mg/day per os) and, after informed consent, biosynthetic GH (2 U/day sc) at bedtime was soon started. Dextrose infusion was gradually reduced and eventually suspended 4 days after beginning continued hormone treatment. No further episode of hypoglycemia occurred in the following 3 days, and he was discharged from the hospital in apparent good condition with instructions for blood glucose self monitoring and glucagon use in the case of severe hypoglycemia.

In the following month only one episode of hypoglycemia was reported. The patient was admitted again to the hospital for control (Table 1). Blood glucose levels were low only sporadically, especially during afternoon and the night. The patient showed a state of relative well-being and no relevant side-effect of GH treatment. The prednisone and GH dose were reduced to 10 mg and 1.5 U/day, respectively. Three months later the patient decided to discontinue GH treatment because of concern of an effect on tumor growth. The patient's condition rapidly worsened, with increasingly frequent episodes of hypoglycemia, and iv glucose treatment was again required. The patient died 5 months later.

It has been reported that mesenchymal tumors may produce and release an excessive amount of IGF-II as well as the isoform called big IGF-II (1). This high molecular weight IGF-II is considered the causative agent of NICTH because of its insulin-like effect, exherted primarily by stimulating glucose uptake at peripheral tissue level (2). In addition, the increased serum IGF-II inhibits both GH and insulin secretion and, as a consequence, lowers the plasma concentration of insulin and GH-dependent IGF binding proteins (mainly IGFBP-3). This in turn increases the unbound IGF-II fraction and worsens its hypoglycemic effect (3).

When surgical removal or radiotherapy is not advised, many other strategies may ameliorate a patient's severe hypoglycemia, including corticosteroid administration (which, in addition to its antihypoglycemic action, may also suppress IGF-II production by the tumor) (4) and subcutaneous glucagon infusion (5). GH treatment has also been tried in such patients (6, 7), with the postulated mechanism of reducing IGF-II availability to tissues by increasing IGFBP-3 levels and the acid labile subunit (ALS) that will form the "ternary complex" containing bound (biologically nonactive) IGF-II. In vitro GH does not appear to have any significant mitogenic effect (8, 9). Increased cancer prevalence in acromegaly is probably a consequence of elevated IGF-1 levels (10). In our patient, however, plasma IGF-1 remained low during hGH treatment at the doses used (Table 1).

In this very severe case of NICTH the combined treatment with prednisone and GH proved effective in ameliorating the hypoglycemic syndrome without side-effects. It can therefore be proposed as a cost-effective palliative treatment in these patients.

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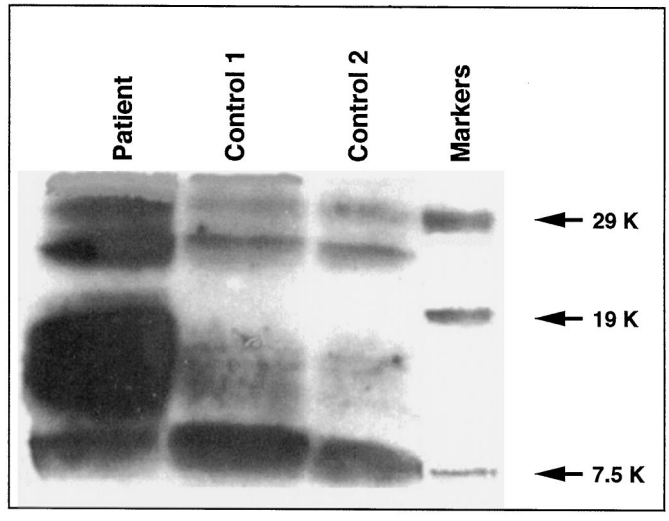

FIG. 1. Western blot analysis of IGF-II of the patient. After acid-ethanol extraction of 300 μL of serum, IGF-II was immunoprecipitated with an anti IGF-II antibody 2H-11 conjugated resin. The samples were solubilized, electrophorezed, and analyzed by an anti-IGF-II antibody (2H-11). Immunoblotting indicates that the serum of the patient shows an abundance and a size-heterogeneity of IGF-II compared with control serum. The molecular weight was between 10–17 kDa, rather than the 7.5 kDa found in two normal control subjects.

TABLE 1. Hormonal measurements before and after 1 month therapy with GH, 2 U/day sc, and prednisone, 15 mg/day po (m ± SD of 4 different measurements)

	Insulin (mU/mL)	GH (ng/mL)	IGF-1 (ng/mL)	IGF-II (ng/mL)	IGFBP-3 (μg/mL)
Basal	4.5 ± 2.5	0.4 ± 0.5	27.8 ± 5.8	1633 ± 98	0.8 ± 0.3
After 1 month	4.5 ± 3.1	1.8 ± 0.3	48.9 ± 1.8	1772 ± 53	1.7 ± 0.4

Normal values. Insulin: 2–10 μU/mL; IGF-I: 78–250 ng/mL (age 40–70); IGF-II: 290–740 ng/mL; IGFBP-3: 1.7–4.0 μg/mL. Assay performed with standard commercial immunoassays.

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Trading One "Dangerous Dogma" for Another? Thyroid Hormone Treatment of the "Euthyroid Sick Syndrome"[b]

To the editor:

In his review of the euthyroid sick syndrome (ESS), Dr. DeGroot (1) cites a litany of circumstantial evidence ostensibly supporting a state of underlying hypothyroidism in patients with systemic illness, which in his view justifies treatment with thyroid hormone. DeGroot argues with the dogma against such treatment espoused by Chopra *et al*. (2) by stating that "there is no factual basis for this dogma," while failing to fully acknowledge that there is no factual basis for treatment either. Surely, a causal relationship cannot be inferred from the association of low serum T4 and risk of death, as severity of illness correlates directly with either low T_4 or risk of death. While he cites the study of Maldonado *et al*. (3), he overlooks their finding that only low T_3 significantly and independently predicted survival beyond what was clinically apparent to intensivist physicians. By definition, the ESS or "low T_3 syndrome" is characterized by low TT_3. Recently, Chopra (4) observed normal free T_3 in 83% of ESS patients and concluded it might be responsible for maintaining their euthyroid state. DeGroot would have us conclude that there is also low FT_4 in ESS, but his own literature review concludes that FT_4 may be low, normal, or elevated.

Our concept of metabolic status in the ESS is that patients are indeed euthyroid during caloric deprivation, acute illness, surgery, and dozens of other models, and that the changes in thyroid function tests reflect effects by the various cytokines, circulating inhibitors, etc., as have been reviewed (1, 5–7). DeGroot calls the normal to low TSH levels in these situations "inappropriately low," rather than considering them appropriate because the patients are euthyroid. He postulates that ESS patients are hypothyroid on the basis of low TRH with secondarily low TSH, while ignoring the fact that observed changes in iodothyronines occur too rapidly in acute illness to be on a hypothalamic/pituitary basis. Indeed, studies by Faber *et al*. (8) indicated that pituitary function was normal in critical illness in the absence of dopamine therapy. DeGroot cites the increases in TSH that may be seen with recovery (9) as "strongly suggesting" that the patients are recovering from a hypothyroid state. This could be true in some states of *prolonged* systemic illness that may lead to relative thyroid hormone deficiency as a result of chronically low degrees of TSH-driven thyroid hormone biosynthesis. In patients such as those with prolonged coma, thyroid hormone therapy might be warranted, and in this context Van den Berghe *et al*. (10) carefully make the distinction between effects of acute *vs.* prolonged systemic illness. But how can thyroid hormone treatment be justified by DeGroot for all patients with altered thyroid function tests of the ESS, which simply reflect acute homeostatic mechanisms when he acknowledges that hypothyroidism may take 2–3 weeks to actually develop? While the review cites studies showing reduced TRH biogenesis, this does not refute a concept of ESS as homeostatic in nature, nor does it imply that the patients are, by definition, hypothyroid. DeGroot suggests the possibility of treating such patients with recombinant human TSH to normalize their serum T_4, but wouldn't L-thyroxine be both considerably more practical and cost-effective?

Finally, DeGroot admits that "proof that tissues are chemically hypothyroid is clearly lacking," yet he concludes that thyroid hormone treatment "may be beneficial" and proceeds to give guidelines for such therapy. He avers that "there is no clear evidence that administration of replacement T_3 . . . is disadvantageous," choosing to ignore critical analyses that caution us otherwise (5–7, 11). We agree with DeGroot when he "cannot envision that replacement of T_3 or T_4 would cure all patients", but the contention that such treatment would cure any is bewildering. He seems to eschew the premise and the evidence that it is the underlying illness (causing the ESS) that needs curing, not the aberrated thyroid function tests. In treating the ESS with thyroid hormone, DeGroot asserts that he would "do no evil," but confesses uncertainty as to whether benefit or harm might ensue. We do agree with him on one point, *i.e.* that large, prospective, carefully controlled studies are needed. To treat with thyroid hormones without such data would certainly not be doing "evil," but could instead represent a misguided attempt to do good that is inconsistent with *primum non nocere*, a dogma that few would characterize as dangerous.

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Dangerous Dogmas in Medicine—Author's Response[c]

To the editor:

I can only plead guilty to many of the charges raised by Drs. Wartofsky, Burman, and Ringel in their comment (above) on my "litany" (defined as: to pray; or, a series of solemn invocations) about Nonthyroidal Illness Syndrome (NTIS). Indeed, I certainly can not prove that a correlation between low T_4 and death implies causation, but to me it

[b] Received January 22, 1999. Address correspondence to: Leonard Wartofsky, Department of Medicine, Washington Hospital Center, 110 Irving Street, NW, Washington, DC 20010-2975.

[c] Received February 17, 1999. Address correspondence to: Leslie J. DeGroot, M.D., Department of Medicine, Thyroid Study Unit, The University of Chicago Medical Center, 5841 S. Maryland Avenue, Mail Code 3090, Chicago, Illinois 60637.

hardly suggests good adaptation. Nor can I prove that treatment is beneficial—only that it makes sense based on all available evidence, is not harmful, and may be helpful.

It is also true that I suggest the TSH responses are inappropriately low (considering the appropriate response to a drop in thyroid hormone levels to be an elevated TSH). And if I left out references to articles by the correspondents that repeat the usual dogma, I apologize.

Wartofsky *et al*. believe that patients with NTIS are euthyroid, although they do concede that a prolonged systemic illness "may lead to relative hormone deficiency as a result of chronically low degrees of TSH-driven thyroid hormone biosynthesis." They state that the "changes in iodothyronines occur too rapidly in acute illness to be on a hypothalamic/pituitary basis." If their reference is to the sharp drop in serum T_3, seen for example after operations, please note that I discussed the important role of reduced T_4 to T_3 deiodination in NTIS. I am not aware, however, of studies showing the time course of development of the low T_3-low T_4 state that characterizes severe NTIS and that is the condition associated with high mortality. I quite agree that cytokines play a role, as clearly stated in my review, perhaps acting on the hypothalmus or peripheral tissues to reduce hormone supply. As for the role of a "circulating inhibitor," I supplied the data indicating that this material cannot be a major factor explaining serum hormone alterations in NTIS. So far as the time it takes to become hypothyroid, I stated that it takes 2–3 weeks after stopping hormone supply for clinically apparent changes to develop. However it is reasonable to believe that the tissue metabolic changes could start as soon as the hormone level drops below normal.

I did not advise treatment with TSH, as the probable response would be mainly T_4 secretion. Nor would I give T_4 as the primary treatment, as they suggest, as it is largely converted to rT_3 in patients with NTIS. The current therapy, if any, should be T_3.

What continues to amaze me is their unquestioning adherence to the dogma that this syndrome is a beneficial adaptation, (a form of euthyroidism, as indicated by the correspondents) when the evidence so strongly indicates a centrally mediated reduction in thyroid hormone production and supply at the tissue level. They refer to "altered thyroid function tests of the ESS which simply reflect acute homeostatic mechanisms." Because there is no proof for this concept, it is only by revelation that one can know the changes are homeostatic, especially when the subjects die.

The authors seriously distort my position on the possible benefits of treatment. As stated in my review, replacing T_3 is not done to "cure" the patients, any more than adjusting the flow of oxygen or giving blood would by themselves cure the patient. But the totality of evidence indicates (and only further study will prove or disprove) that replacement of thyroid hormone is one of many actions taken in the care of these seriously ill patients that may improve their chance of recovery.

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Comment on Association between Insulin-Like Growth Factor-I (IGF-I) and Bone Mineral Density: Further Evidence Linking IGF-I to Breast Cancer Risk[d]

To the editor:

The study by Langlois *et al.* (1) demonstrated an intriguing association between insulin-like growth factor I (IGF-I) and bone mineral density (BMD) in older women. Serum IGF-I levels were positively associated with BMD in all five bone sites, and the association remained statistically significant after potentially confounding factors were adjusted in the analysis, including age, body mass index (BMI), mobility limitation, smoking, and estrogen use. This finding not only suggests the impact of IGF-I on the balance between bone resorption and formation, but also provides evidence to the involvement of IGF-I in breast cancer risk. Both BMD and IGF-I are found to be associated with the risk of the disease.

Cauley *et al.* (2) reported in 1996 that BMD was associated with the risk of breast cancer in older women. In the study, BMD was measured in five bone sites, including proximal radius, distal radius, calcaneus, total hip, and total spine. The risk of breast cancer was increased significantly with BMD in three of the five bone sites measured. The association was sustained after adjusting for possible confounding factors such as age, BMI, exercise, alcohol consumption, and smoking. When the BMD data was compared between the highest and lowest quartile groups, the increase in breast cancer risk with BMD was significant in all five sites. Given a strong link between estrogen and BMD as well as estrogen's role in breast cancer, this association was interpreted as an indication of intensive exposure to endogenous estrogens.

Although an alternative explanation of IGF-I in the association of BMD and breast cancer risk was mentioned in the paper, evidence regarding the role of IGFs in breast cancer from epidemiologic studies was not sufficient at that time. Most of the studies were *in vitro* or *in vivo* lab experiments. Population-based studies were scarce, only one case-control study and one small clinical study (3, 4). Despite the fact that both of the studies suggested high plasma IGF-I to be associated with an increased risk of breast cancer, a temporal relationship between IGF-I and breast cancer could not be determined, as they were case-control comparisons.

During the past two years, the understanding of IGF in breast cancer has improved substantially. There has been growing evidence linking the IGF family to the development and progression of breast cancer. First, in addition to having strong mitogenic effect on breast cancer cells, IGFs also have antiapoptotic impact on breast cancer cells, thereby facilitating the growth (5). Second, IGFs interact with molecules that are involved in breast cancer. IGFs and estrogens have a synergistic interaction on the growth of breast cancer. Estrogens induce the expression of IGF-I and the IGF-I receptor, and IGFs enhance the transcription activation of estrogen receptor (6). Antiproliferative molecules wild-type p53 protein, retinoic acid, vitamin D, and transforming growth factor β exert their actions through up-regulating the expression of the IGF binding proteins, which in turn suppress the mitogenic action of IGFs (7–9). Finally, a recent prospective cohort study demonstrated that high IGF-I levels in plasma were associated with an increased risk of breast cancer (10). Because the blood samples were collected long before the development of the disease, findings from this type of study were more compelling than the case-control studies.

The association of BMD with IGF-I provides further evidence to support the involvement of IGF-I in breast cancer, as the relationship appears to be an additional mechanism, in addition to estrogen, underlying the association between BMD and breast cancer risk. Given the role of IGF-I in breast cancer and the induction of IGF-I production by growth hormone (GH), the recommendation of GH replacement therapy to prevent osteoporosis or to improve other health issues may be premature. More studies are needed to further assess the nature of the relationships among IGF-I, BMD, and breast cancer risk. Determining a safe maximum concentration of IGF-I in blood after balancing the benefits and potential hazards of the molecule would be a crucial issue in future GH replacement therapy.

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Association between Insulin-Like Growth Factor (IGF-I) and Bone Mineral Density: Further Evidence Linking IGF-I to Breast Cancer Risk—Authors' Response[e]

To the editor:

We thank Dr. Yu for his thoughtful letter (above) summarizing the evidence for the associations among insulin-like growth factor-I, bone mineral density (BMD), and risk of breast cancer. In addition to the research mentioned above, data from the Framingham Heart Study also showed a strong positive association between BMD and risk of breast cancer (1). Although the findings to date are provocative, there are many unanswered questions. First, it has not yet been established that IGF-I levels are causally linked to breast cancer risk. Clearly, IGF-I is a growth factor that can promote mammary cell mitogenesis, but the precise relationship of this circulating peptide to local tumor development is not clear (2). Second, total serum levels of IGF-I may NOT reflect tissue bioactivity and therefore may be at best only a surrogate predictor of IGF-I activity at the cellular level. In particular tumor cells, there are several autocrine and paracrine networks that include IGF-I, IGF binding proteins (IGFBPs), and IGFBP-specific proteases. All or some of these proteins can promote neoplastic growth, but their activity cannot be discerned through measurement of circulating concentrations (2). Third, little is known about the status of the IGF type I receptor in relation to lifetime high or low IGF-I exposure at the tissue level (2). In sum, IGF-I is only one component of a complex and redundant network that almost certainly affects the pattern and activity of various tumors. Whether total serum levels of IGF-I provide an integrated assessment of this activity remains to be determined. We do agree that further research to delineate the relationships among IGF-I, BMD, and breast cancer risk is needed to determine the safety of growth hormone replacement therapy.

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Comment on Long-Acting Lanreotide Inducing Clinical and Biochemical Remission of Acromegaly Caused by Disseminated GHRH Secreting Carcinoid[f]

To the editor:

In the September 1998 issue of JCEM, Drange and Melmed (1) reported on the use of long-acting somatostatin analogue, lanreotide, in ectopic GHRH syndrome due to a bronchial carcinoid. A similar case was presented by us at 1997 Meeting of Polish Endocrine Surgeons in Warsaw (2). We would like to comment briefly on lanreotide treatment in ectopic acromegaly.

A 40-yr-old man was referred to our institution for the evaluation of acromegaly and thyroid tumor. At the age of 13 the patient had undergone a left inferior lobectomy for a bronchial carcinoid. Since the age of 20, a slow, gradual development of typical acromegalic features had been noted by the patient, but he did not seek medical advice. At 37, because of hemoptysis, he was admitted to the regional hospital where the recurrence of carcinoid was diagnosed by computed tomography scan, with the large tumor infiltrating both main bronchi just below the bifurcation. The tumor was considered inoperable.

On admission the patient had typical acromegalic features with a 2-cm tumor of the left lobe of thyroid gland. The endocrine evaluation showed elevated GH and IGF-I levels: 130 μg/L and 1380 μg/L, respectively. Prolactin and α-subunit levels were also elevated: 74 μg/L and 15.0 μg/L, respectively. The urinary excretion of 5-HIAA was 73.5 μmol/g creatinine per day. The pituitary hyperplasia was noted on magnetic resonance imaging scan without evidence of pituitary tumor. Multiple liver metastases were demonstrated on computer tomography scan. These findings combined with the patient's history were highly suggestive of an ectopic GHRH secretion by the bronchial carcinoid tumor. This was confirmed by the very high GHRH level: 9.2 μg/mL (normal values < 0.1 μg/mL). GHRH was determined by Professor Klaus von Werder (Schlosspark Klinik, Berlin, Germany).

As the thyroid tumor was typical of apudoma on cytologic examination, and calcitonin levels were normal we decided to perform a total thyroidectomy. The carcinoid's metastasis was demonstrated in the resected tumor on pathologic examination. The removal of the thyroid tumor resulted in the fall in GHRH level to 6.1 μg/L.

At this point the diagnosis of the cetopic GHRH syndrome seemed certain. We started with lanreotide (Somatuline, Ipsen Beaufour, France) 30 mg im, every 2 weeks. After 20 weeks GHRH levels dropped to 3.5 μg/L, while the GH level fell to 14 μg/L. GH was estimated before every injection of lanreotide. We observed a gradual fall in GH levels during lanreotide therapy: 99 μg/L at 2 weeks, 80 μg/L at 4 weeks, 35 μg/L at 10 weeks, and 14 μg/L at 20 weeks of the therapy. The lanreotide therapy resulted in a marked and sustained clinical improvement. The patient reported a dramatic fall in perspiration and an increased sense of well-being. On magnetic resonance imaging scan, the volume of the pituitary decreased by one third at the end of 20-week treatment. No side-effects of lanreotide therapy were observed.

It is worth noting that the effect of lanreotide on GH was more pronounced than that on GHRH. In our patient GH levels decreased 8-fold during lanreotide therapy, while GHRH levels decreased only 2-fold. This may suggest a direct effect on pituitary that corroborates the recent reports on the beneficial effect of lanreotide therapy as the preparation for the neurosurgery for pituitary tumors (3).

We conclude that long-acting somatostatin analogues are the drugs of choice in the ectopic GHRH syndrome, and the evaluation of GH levels is more reliable in defining the results of the treatment than GHRH determination.

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Is the Prevalence of Addison's Disease Underestimated?[g]

To the editor:

The clinical spectrum of Addison's disease has changed dramatically over the last 30 years, and autoimmunity is now the most common cause of primary adrenal insufficiency in Western countries (1). Using an original flowchart of immune and biochemical markers, we have shown that adrenal autoantibodies are present in 70% of Addison patients (2). Furthermore, approximately 1% of patients with endocrine autoimmune disorders have clinical or subclinical signs of adrenal insufficiency (3). In spite of the availability of accurate biochemical and immune markers of Addison's disease, its prevalence in the general population has not been widely investigated. In initial studies (4–5), the prevalence of Addison's disease in Western countries was calculated at 35–60 per million. However, the results of a recent study (6) suggest that this disease could be more common than previously reported.

To accurately evaluate the prevalence of Addison's disease in the general population, we selected a geographically delimited region of central Italy, Umbria, and we determined the total number of subjects suffering from Addison's disease, during the period January 1–December 31, 1996 in this region. According to the Italian Institute of Statistics (ISTAT), the population resident in Umbria is 811,887 (394,211 males and 417,676 females). We used the clinical records of the patients attending the endocrine unit of our department as the primary data source. Because cortisone acetate is the only treatment for Addison's disease available in Italy, given the unavailability of oral preparations of hydrocortisone, we used the regional computerized file of the prescriptions of cortisone acetate as a secondary and independent source. Diagnosis of Addison's disease was confirmed by interviewing the treating physicians and by following standard criteria (1).

The primary source identified 59 Addison patients and the secondary source 234 subjects in treatment with cortisone acetate. Of these latter 234 subjects, 91 had Addison's disease, and 55 of them had already been identified by the primary source. The remaining 143 subjects identified by the secondary source had either secondary adrenal insufficiency or a neoplasm impairing adrenal function. Overall, the two data sources identified a total of 95 (42 males and 53 females) Addison patients, and the combined case ascertainment was 97% as calculated by capture-recapture analysis. The resulting prevalence of Addison's disease in the general population was 117 per million (95% confidence interval: 95–143). Prevalence among males and females was 106 per million (95% confidence interval: 77–144) and 127 per million (95% confidence interval: 95–166), respectively.

The frequency of Addison's disease in our study represents the highest prevalence reported so far, and it is 2- to 3-fold higher than those previously reported in other studies (4, 5). Our results indicate that the prevalence of Addison's disease has so far been underestimated. Given the increase in frequency of adrenal autoimmunity in Addison patients observed over the last 20 years, we hypothesize that the incidence and prevalence of autoimmune adrenal insufficiency is rising. Additional population-based studies are needed to monitor the yearly incidence of this disease and to test this latter specific hypothesis.

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