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RAPID PUBLICATION

High prevalence of biochemical acromegaly in primary care patients with elevated IGF-1 levels

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Summary

Objective The estimated prevalence of acromegaly is 40–125 per million. The diagnosis of acromegaly is often delayed due to deficits in recognizing the signs of the disease. It is not known how many subjects with increased IGF-1 levels have acromegaly. We aimed to assess the prevalence of acromegaly in primary care by screening for elevated IGF-1 levels.

Design A cross-sectional, epidemiological study (the DETECT study).

Patients A total of 6773 unselected adult primary care patients were included.

Measurements We measured IGF-1 in all patients and recommended further endocrine evaluation in all patients with elevated IGF-1 levels (> 2 age-dependent SDS).

Results Of 125 patients with elevated IGF-1 levels, 76 patients had indeterminate results and acromegaly could be excluded in 42 patients. One patient had known florid acromegaly. Two patients had newly diagnosed acromegaly and pituitary adenomas. Four patients had biochemical acromegaly but refused further diagnostics. This corresponds to a prevalence of 1034 per million patients.

Conclusions Our study shows a high prevalence of undiagnosed acromegaly in primary care. These results imply that acromegaly is underdiagnosed and stress the importance of detecting acromegaly.

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Introduction

The symptoms of acromegaly arise due to elevated levels of GH and its peripheral hormone IGF-1. This is caused by a GH-secreting pituitary adenoma in most cases or, less commonly, by ectopic causes of GH-releasing hormone or GH secretion. The prevalence of acromegaly has been estimated to be 40–70 per million in the population.[1] In a more recent analysis, a prevalence of 125 per million was found.[2] Acromegaly is associated with increased mortality and, mainly cardiovascular and skeletal, morbidity.[3] Due to the slow-onset and progress of symptoms, and to the fact that many physicians are unfamiliar with the disease, there is normally a delay of 7–10 years between onset of the first symptoms and the diagnosis of acromegaly.[3] It has never been assessed as to how many subjects with increased IGF-1 levels, regardless of clinical presentation, actually have acromegaly. The aim of this study was to assess the prevalence of acromegaly in primary care patients by screening for elevated IGF-1 levels.

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Methods

DETECT is a large, multistage, nationally representative, cross-sectional study of 55 518 unselected consecutive patients (59% women and 41% men; over 17 years) in 3188 primary care practices in Germany with a prospective component in a random subset of 7519 patients and 851 primary care settings. The initial physicians' response rate was 60·2% and further adjustments for nonresponse, regional distribution, and attrition were performed. During a specified half a day in September 2003, all patients attending the primary care practice were asked to participate in the study. For all patients, a comprehensive standardized clinical evaluation (patients' self-report and physicians' assessments) was conducted. Patients in the prospective subset were additionally characterized by an extensive standardized laboratory program focusing on CV risk assessment. For technical reasons, IGF-1 measurements were available only in 6773 patients (4013 women and 2760 men). These patients constituted the sample studied here. With regard to disease and risk status, the patient group studied here was comparable to the laboratory subsample and the total DETECT sample. Further details are available at <http://www.detect-studie.de> and in.[4,5] The study was approved by the ethics committee of the Technical University of Dresden. All patients gave written informed consent.

Blood samples were collected and shipped by courier at room temperature within 24 h to the central laboratory at the Medical University of Graz (Austria). Upon arrival in the central laboratory, the samples were centrifuged immediately and the serum was stored at –20 °C until further processing. IGF-1 was determined with an automated chemiluminescence system (Nichols Institute Diagnostics,

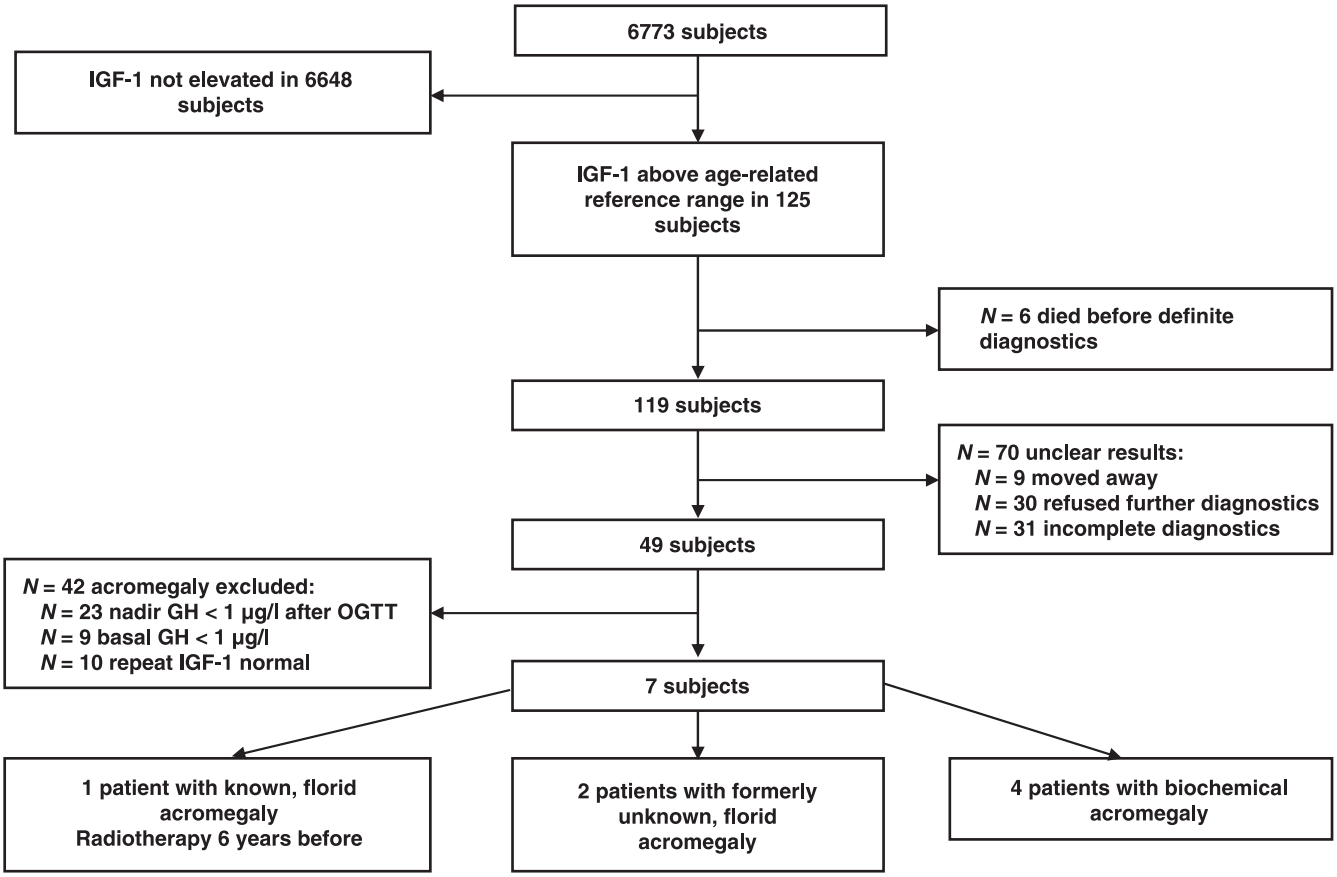

Fig. 1 Diagnostic work-up of primary care patients with IGF-1 measurement.

San Clemente, CA). The maximal intra- and interassay coefficients of variation were 5% and 7%, respectively. Reagents and secondary standard were used as recommended by the manufacturer. Sex- and age-dependent reference ranges IGF-1 (normal range between –2 and +2 SDS) for this assay were established in a large group by Brabant *et al.*[6] We transformed IGF-1 levels to IGF-1 SDS according to Brabant *et al.*[6] and regarded IGF-1 levels above +2 SDS as elevated.

The attending physicians of patients with elevated IGF-1 levels were contacted twice by letter, and up to two times by telephone, within the following 30 months. We recommended further testing with an oral glucose tolerance test and basal IGF-1 measurement and asked the physicians to send us the results. We excluded acromegaly if basal GH or GH nadir was < 1 µg/l after glucose load, or if repeat IGF-1 was below the upper age-related reference limit of the local laboratory. A GH nadir after glucose load, or a paradoxical increase ≥ 1 µg/l in combination with repeat IGF-1 above the age-related reference range was considered as biochemical acromegaly and pituitary imaging was recommended. If only basal values with GH ≥ 1 µg/l, or IGF-1 above age-related reference ranges were available, acromegaly was neither excluded nor diagnosed.

Results

Among subjects with elevated IGF-1 levels, IGF-1 and IGF-1 SDS ranged from 177 to 961 µg/l and 2·0–7·0, respectively (mean ± SD: 287 ± 110 µg/l and 2·5 ± 0·8, respectively). Figure 1 shows that of 125 patients with elevated IGF-1 levels, 76 patients had indeterminate results and acromegaly could be excluded in 42 patients. The remaining seven patients had biochemical acromegaly. One patient (Female, 54 years, IGF-1351 µg/l, 2·85 SDS) had known florid acromegaly and had received irradiation for a pituitary adenoma 6 years earlier. In two patients (Female, 50 years, IGF-1962 µg/l, 6·85 SDS, GH nadir 2·3 µg/l and F, 66 years, IGF-1780 µg/l, 6·5 SDS, GH nadir 28·4 µg/l), acromegaly was previously not known and newly diagnosed. The first patient reported headaches, increased finger size, type 2 diabetes and had had a thyroidectomy 4 years before. A microadenoma of the pituitary was found and surgery recommended. The latter patient had hypertension, type 2 diabetes, sleep apnea syndrome, a history of surgery for papillary thyroid carcinoma and uterus myoma, and an increase in size of hands and feet in the last 6 years. A pituitary macroadenoma (shown in Fig. 2) was found and operated. The patient reported a significant improvement in the quality of life after surgery.

Another four patients had nonsupressed GH and elevated repeat IGF-1. In one of these patients, cranial Mr imaging showed no sign of a pituitary adenoma but the quality of sella imaging was not reported. The other three patients refused further diagnostics due to lack of clear-cut clinical signs of acromegaly. Table 1 summarizes the clinical features of the patients with biochemical acromegaly. Assuming that only these 7 out of 6773 patients had acromegaly we estimated a prevalence of 1034 acromegalics per million patients in primary care.

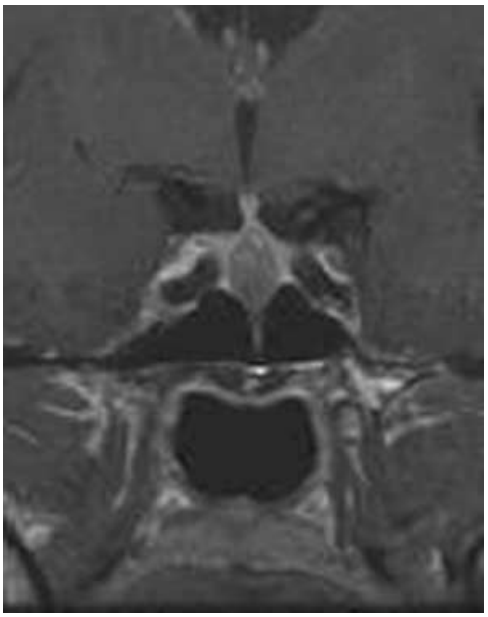

Fig. 2 Frontal magnetic resonance image of the sellar region of a 66-year-old female patient with acromegaly. Macroadenoma of the pituitary.

Discussion

To our knowledge, this is the first study that aims to calculate the prevalence of acromegaly in a specified population by biochemical assessment of all subjects rather than by screening for clinical signs. With this approach we were also able to detect cases of acromegaly that could not be detected otherwise either due to lack of clear-cut specific symptoms or failure of the patients or attending physicians to recognize specific symptoms. By definition, healthy subjects can also have hormone levels outside of the normal range, as a normal range excludes subjects with levels above +2 SD or below –2 SD. Elevated IGF-1 levels are therefore not necessarily pathological. On the other hand, it is clear that pathological states associated with IGF-1 oversecretion accumulate among subjects with elevated IGF-1 levels.

We can not exclude a preselection due to screening only primary care patients. Our prevalence estimate is, thus, only valid for primary care and not the general population. However, considering that six out of seven patients who we identified with biochemical acromegaly were previously not diagnosed acromegalic, this estimate is still significantly higher than expected. Moreover, in the majority of patients, we could neither diagnose nor rule out acromegaly with certainty, making it likely that the real number of undiagnosed acromegaly is even higher. Even if we assume that there were no further cases of acromegaly among the patients with unclear results, we found the prevalence of acromegaly in primary care to be 10–20 times higher than previously estimated in the general population.

Due to the limitations of an epidemiological, noninterventional study, endocrine testing and GH assays, following the initial measurement of IGF-1 in our central laboratory, were not standardized. However, this reflects every-day clinical practice in outpatient care. Moreover, the guidelines for the treatment of acromegaly do not apply to a specific GH assay.[7] Our study is further limited by the fact that three out of seven patients with biochemical acromegaly refused further imaging studies, thus, making it impossible to locate the cause of GH oversecretion. MR imaging was performed in another patient, but no pituitary adenoma was detected, though, this does not exclude acromegaly. It is possible that this patient had a GH

Table 1. Clinical features of the patients with biochemical acromegaly

Sex	Age	Diagnostic status on acromegaly	IGF-1	IGF-1 SDS	Repeat IGF-1 xULN	GH nadir OGTT	MRI findings	Acromegalic features	Other diseases
M	80	New	254	2·60	1·66	3·7	ND	No	Diabetes, dyslipidaemia, thyroid disease, chronic kidney failure, liver disease, depression
F	80	New	239	2·76	1·61	2·4	ND	No	Dyslipidaemia, hypertension, arthritis, depression, osteoporosis
F	62	New	337	3·07	1·66	4·5	ND	No	None
F	74	New	223	2·27	1·22	1·3	Normal	No	Diabetes, dyslipidaemia, CAD, CLL
F	50	New	961	6·85	9·55	2·7	Microadenoma	Increased finger size, face changes	Diabetes, dyslipidaemia, hypertension, thyroidectomy, hysterectomy
F	66	New	780	6·51	4·37	24·9	Macroadenoma	Increased finger and foot size, face changes	Diabetes, dyslipidaemia, hypertension, papillary thyroid cancer, myoma, sleep apnea syndrome
F	54	Known	351	2·85	ND	ND	ND	ND	Hypertension, CAD, arthritis

Calculated according to[6] ULN, upper limit of normal range; OGTT, oral glucose tolerance test; MRI, magnetic resonance imaging; ND, not done; CAD, coronary artery disease; CLL, chronic lymphatic leukaemia.

secreting microadenoma below the detection limit, or an ectopic cause of GH oversecretion.

Several causes other than acromegaly need to be considered in the interpretation of dynamic GH testing. Nonsuppressed GH can also occur in renal insufficiency, liver failure, active hepatitis, hyperthyroidism, diabetes mellitus or malnutrition. However, without acromegaly, IGF-1 would be either normal or low in these conditions.[8] All of our patients with nonsuppressed GH levels also had elevated IGF-1 levels in at least two measurements, confirming acromegaly biochemically in these patients. One patient had chronic kidney disease. Even though biochemical assessment of acromegaly is complicated by this fact, nonsupppressed GH secretion due to renal failure was always associated with low or normal, but not elevated IGF-1 levels in the literature[9,10] to our knowledge.

It is interesting that some patients with biochemical evidence of acromegaly developed no clear-cut symptoms of acromegaly. It appears that these patients have a preclinical or subclinical form of acromegaly. In about 0·5% of autopsy studies in the normal population, pituitary adenomas that stain positive for GH have been found, even though the prevalence of clinical acromegaly has been estimated to be much lower.[1] Possibly, this corresponds to our findings of biochemical acromegaly without clear-cut clinical signs in some patients. It is not clear whether these patients will develop the clinical signs and complications of acromegaly and whether they would benefit from further diagnostics and treatment.

However, at least two patients clearly benefited from the diagnosis in our study. This study was not designed to assess the cost-effectiveness of IGF-1 screening in the general population or primary care. Thus, our data do not allow a general recommendation or discouragement of IGF-1 screening for the population. Nevertheless, our findings suggest that acromegaly is clearly underdiagnosed in primary care. We urgently need strategies for a better diagnosis of acromegaly and its complications.

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