ORIGINAL ARTICLE

Establishment of reference values for endocrine tests. Part VII: Growth hormone deficiency

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ABSTRACT

Background: Plasma insulin-like growth factor (IGF-I) concentration can be used as a rough indicator of the growth-hormone status. However, for the diagnosis of growth hormone deficiency, dynamic tests are required. The growth hormone (GH) response in the insulin tolerance test (ITT) is considered to be the gold standard in this respect. An alternative for the ITT is the GHRH/GHRP-6 test, which has fewer side effects. In this study we established reference values for IGF-I levels and for the GH response in both dynamic tests.

Methods: We studied 296 subjects recruited from the general population, equally distributed according to sex and aged between 20 and 70 years. Serum IGF-I level was measured in all subjects and an insulin tolerance test (0.15 U/kg Actrapid iv) and GHRH/GHRP-6 test (1 μg GHRH/ kg and 1 μg GHRP-6/kg) were performed in 49 subjects.

Results: In multivariate analyses both IGF-I and the GH response in the ITT were significantly influenced by age, whereas the GH response in the GHRH/GHRP-6 test was significantly affected by BMI. There was no sex difference in IGF-I and in the GHRH/GHRP-6 test, but in the ITT males had a higher GH peak. There was a significant correlation between the GH responses in both tests, and the GH response was significantly higher in the GHRH/ GHRP-6 test than in the ITT. Age-adjusted reference values were established for each test.

Conclusion: We have established age-adjusted reference values for serum IGF-I and for the GH response in the ITT and GHRH/GHRP-6 test.

KEYWORDS

Growth hormone deficiency, insulin tolerance test, GHRH/ GHRP-6 test, IGF-I

INTRODUCTION

Growth hormone deficiency (GHD) in adults is characterised by changes in body composition that include decreased lean muscle mass, muscle strength and exercise performance, and increased body fat mass. In addition, metabolic derangements and a decrease in bone mineral density are known to occur in this setting. There is also an association with a diminished quality of life. Administration of growth hormone replacement has shown to provide physical and psychological improvement.[1-5] A correct diagnosis in the evaluation of patients for suspected GH deficiency is essential. For, in case of a false-positive diagnosis, the patient will be subjected to a prolonged and expensive treatment, whereas a false-negative diagnosis will deprive the patient of treatment. To identify patients appropriately, there is a need for reliable tests to diagnose GHD.

Plasma insulin-like growth factor (IGF)-I is growth hormone (GH)-dependent and can be used as an indicator of GH status. IGF-I serum level is, however, affected by factors as age, nutritional status, thyroid function and lean body mass. There is significant overlap in IGF-I values between those with and without GHD, and the overlap increases with higher age. Serum IGF-I can be of some diagnostic assistance if levels are below the age-adjusted normal range, but a normal IGF-I result does not exclude a diagnosis of GHD.[4,6-10]

Other biochemical measurements such as IGF-binding protein-3 or mean 24-hour GH concentrations also have limited diagnostic value in adults, because of overlap between healthy individuals and those with a deficiency.[7,9,10]

For these reasons the diagnosis of GHD requires provocative tests of GH secretion.

The insulin tolerance test (ITT) is considered the test of choice. It allows evaluation of the complete hypothalamic-

pituitary-somatotroph axis, making it useful in patients with both hypothalamic and pituitary disease. The ITT has been found to have high sensitivity and specificity in all age groups.[11] However, there are several disadvantages to the ITT. It is associated with uncomfortable side effects and it is contraindicated in patients with seizure disorders or cardiovascular disease. In addition, it requires constant monitoring even in healthy adults, although it is quite safe in experienced hands under adequate supervision.[12] It is established that obesity, in the abdominal region in particular, is associated with a blunted GH response to stimulation. Thus, in overweight patients it may be difficult to distinguish GHD from the decreased responsiveness due to obesity.[13-15]

Although the ITT is considered the gold standard for the diagnosis of GHD, the limitations of this test suggest the need for additional tests, with appropriate cut-off levels, to diagnose GHD. Moreover, in patients with ≤2 known other pituitary hormone deficiencies, two independent stimulation tests are recommended to diagnose GHD in adults.[6,16] An alternative provocative test is the combined administration of GH-releasing hormone (GHRH) plus GH-releasing peptide-6 (GHRP-6). GHRP-6 is a synthetic GH secretagogue that is a very potent and reproducible stimulus of growth hormone secretion. It has previously been reported that the GHRH/GHRP-6 stimulation test was not confounded by body composition.[17] Also, the ability of the GHRH/GHRP-6 test to discriminate between normal GH state and GHD was reported not to be affected by age.[17,18]

The GHRH/GHRP-6 test is free from serious adverse effects, mild flushing being the only side effect encountered. There are no known contraindications to its use.[17,19]

The aim of this study was to establish reference values for the GH peak in the ITT and in the GHRH/GHRP-6 stimulation test. Reference values for IGF-I have previously been published by our laboratory in this journal.[20] However, at that time IGF-I was measured by a chemiluminescent immunoassay from Nichols (Nichols Advantage). Because the manufacturer stopped the production of this kit, we now report reference values for IGF-I on an Immulite 2000 system. This assay is used in the majority of the Dutch hospitals.

SUBJECTS AND METHODS

Subjects

Volunteers were recruited by advertisement in a local newspaper with a free house-to-house distribution in the Amsterdam region and by advertisements in 'Status', the biweekly information bulletin of the University of Amsterdam. We placed an advertisement for subjects who allowed blood samples to be taken to establish reference values for IGF-I and an advertisement for subjects who were willing to undergo a GHRH/GHRP-6 test and an ITT. The subjects were screened for the inclusion and exclusion criteria by telephone and during the intake visit.

The inclusion criteria were age 20 to 70 years and self-reported good health. Exclusion criteria were a medical history of cardiac disease (angina pectoris or cardiac arrhythmias), cerebrovascular disease or neurosurgery, known diabetes mellitus, epilepsy, use of pharmacological doses of glucocorticoids, intravenous drug abuse and pregnancy. Pregnancy was excluded in all female subjects by a urine human chorionic gonadotropin (hCG) test.

IGF-I was measured in 296 subjects (148 women and 148 men, mean age 44.2 years (SD 14.3, range 20 to 70), mean BMI (measured in 246 persons) 25 (SD 4.7, range 18 to 44)).

From them, 49 subjects (25 women and 24 men, mean age 44.6 years (SD 14.6, range 20 to 68), mean BMI 25 (SD 4.6, range 18 to 43)) underwent an ITT and a GHRH/GHRP-6 test. In 36 subjects the ITT preceded the GHRH/GHRP-6 test, the others started with the GHRH/GHRP-6 test. At the intake visit, subjects were interviewed about general health and use of drugs and medication. Two females used oral contraceptives. Information was given about the study and the tests. Weight and height were measured. Informed consent was obtained from all subjects and the study was approved by the hospital's ethics committee.

The dynamic tests were performed at 8.30 am, after an overnight fast. Subjects were in a recumbent position. For all tests an indwelling venous catheter was inserted (t = -30 min) in an antecubital vein. IGF-I was measured in a basal sample.

Insulin tolerance test

Blood samples were taken at t = -15 min and t = 0 min for measuring GH. After the blood sample at t = 0 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. To reduce the inter-laboratory variation, GH assays have been harmonised in the Netherlands. A harmonisation sample from native serum with an assigned consensus value is used for this purpose.

Criteria for a valid test result were neuroglycopenic symptoms lasting for at least ten minutes and a blood glucose concentration of <2.2 mmol/l.

GHRH/GHRP-6 test

After three basal samples at t = -30, -15 and 0 min, the subjects underwent combined administration of GHRH

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plus GHRP-6 as an intravenous bolus injection of 1 μg per kg bodyweight of GHRH (Ferring GmbH, Kiel, Duitsland), immediately followed by an intravenous bolus injection of 1 μg per kg bodyweight of GHRP-6 (Clinalfa Läufelfingen, Switzerland). Further blood samples were obtained at t = 15, 30, 45, 60, 90 and 120 min.

Analytical methods

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% (3.4 mU/l) and 1.8% (20.1 mU/l), and an inter-assay coefficient of variation of 10.9% (3.0 mU/l) and 7.7% (21.7 nmol/l). Conversion factor GH: 1 μg/l = 3.67 mU/l.

IGF- I 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% (9.9 nmol/l) and 2.0% (89 nmol/l), and an inter-assay coefficient of variation of 5.2% (10.6 nmol/l) and 4.1% (55.8 nmol/l).

Statistical methods

The effects of gender, age and BMI on the IGF-I concentration were evaluated with linear regression analysis.

The peak serum GH response was used as the primary variable for analysis of the stimulation tests. The relation between the extent of the hypoglycaemia and the GH peak after insulin was tested with Pearson's correlation coefficient. The relations between age, BMI and gender and the GH peak in the insulin tolerance test and the GHRH/GHRP-6 were tested with linear regression analyses.

Square root transformations of the IGF-I concentration and the growth hormone peak (GH peak) concentrations after insulin injection and after GHRH/GHRP-6 were done to obtain normal distributions. The continuous variables age and BMI were included as linear terms in the model.

The correlations between IGF-I and GH peak in the ITT and the GHRH/GHRP-6 test were tested with Pearson's correlation coefficient and the difference between the GH peaks in the ITT and the GHRH/GHRP-6 test with a paired *t*-test.

We modelled the IGF-I and GH concentrations as a function of age in a flexible way by means of restricted cubic spline functions. Spline functions are used to represent smoothly varying relationships between a predictor (age) and the response (IGF or GH peak), which can take on virtually any shape.[21] Reference values were based on the 95% prediction intervals as obtained from these models.

The SPSS 12.0.2 and R 2.7.0 (R Foundation for Statistical Computing, Vienna, Austria) statistical packages were used. In all analyses, p values <0.05 were considered statistically significant.

RESULTS

Basal plasma levels of IGF-I

The mean IGF-I concentration was 19.1 nmol/l (range 5.0 to 54.0 nmol/l). In a multivariate regression analysis, there was a significant negative influence of age on the IGF-I concentration (β = -0.030 change per year, 95% CI -0.036 to -0.024, p<0.001). The effect of BMI was borderline significant (β = -0.017, 95 % CI -0.035 to 0.000, p=0.05) and there was no effect of gender on the IGF-I concentration (β = 0.016, 95% CI -0.137 to 0.168, p=0.8). The reference values by age are given in *table 1* and *figure 1*.

Insulin tolerance test

No serious side effects were observed with the ITT. During this test all subjects had signs of neurohypoglycaemia; however, two subjects did not have a biochemical hypoglycaemia below 2.2 mmol/l (one 2.3 mmol/l and one 2.4 mmol/l). Nevertheless, they were included in the statistical analysis because their neurohypoglycaemia was evident. The depth of the hypoglycaemia varied from 0.5 to 2.4 mmol/l (mean 1.3, SD 0.4). Hypoglycaemia induced a GH release in all subjects. Most participants reached a GH peak 60 (35%) or 75 (43%) minutes after administration of insulin; 22% already reached the GH peak after 30 or 45 minutes. The GH peak height was not related to the nadir of the hypoglycaemia (r = -0.085, p=0.56).

In a multivariate regression analysis age had a significant negative effect on the GH peak (β = -0.053 change per year, 95% CI -0.099 to -0.008, p=0.02). There was also an effect of gender (β = 1.180, 95% CI 0.070 to 2.289, p=0.04), the GH peak was higher in men (mean 62.8 mE/l, SD 5.0) than in women (mean 46.4 mE/l, SD 4.3). After correction for age and gender, we did not find a significant effect of BMI (β = -0.091, 95% CI -0.236 to 0.053, p=0.2). The reference values are given in *table 1* and *figure 2*.
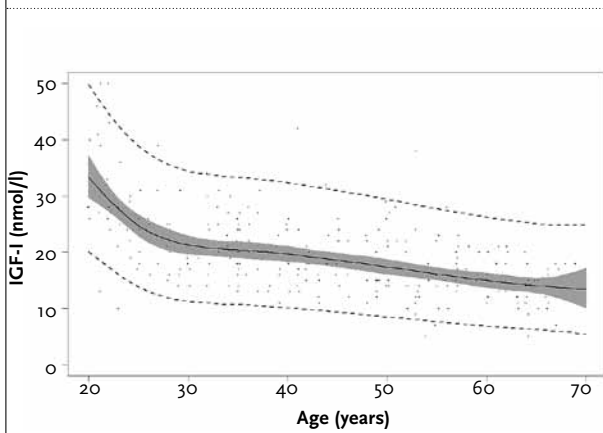
GHRH/GHRP-6 test

Most participants reached a GH peak after 15 (49%) or 30 (45%) minutes, three (6%) had a GH peak after 45 minutes. In a multivariate regression analysis, there was a significant negative effect of BMI on the GH peak (β = -0.529, 95% CI -0.730 to -0.329, p<0.001). The effects of age and of gender were not significant (β = -0.035, 95% CI -0.099 to 0.029, p=0.28 and β = -1.091, 95% CI -2.696 to 0.513, p=0.18 respectively). The mean GH peak was 135.6 mE/l, SD 15.0). The reference values by age are given in *table 1* and *figure 3*.

The IGF-I concentration was not correlated with the GH peak in the insulin tolerance test (r = 0.15, p=0.32). However, the correlation with the GH peak in the GHRH/GHRP-6 test just reached significance (r = 0.28, p=0.048).

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Table 1. *Reference values for plasma IGF-I concentrations (nmol/l) and for GH peak concentrations (mE/l) in ITT and GHRH/GHRP-6 test*
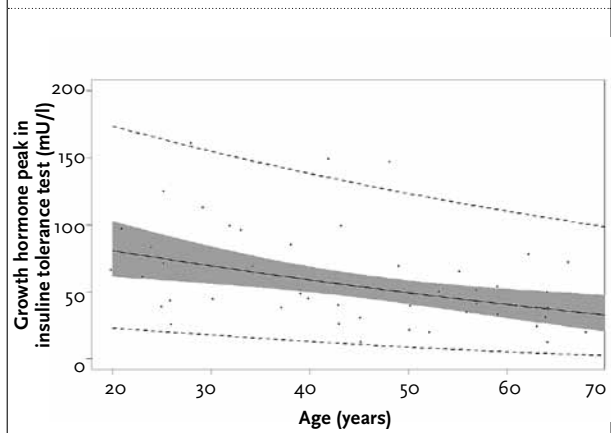
Age (years)	IGF-I P 2.5	IGF-I P 50	ITT P 2.5	ITT P 50	GHRH/GHRP-6 P 2.5	GHRH/GHRP-6 P 50	Age (years)	IGF-I P 2.5	IGF-I P 50	ITT P 2.5	ITT P 50	GHRH/GHRP-6 P 2.5	GHRH/GHRP-6 P 50
20	20.1	33.3	22.9	80.7	54.9	215.4	46	9.2	18.4	10.3	53.1	19.4	131.5
21	18.7	31.3	22.4	79.5	53.3	211.8	47	9.0	18.1	9.9	52.1	18.3	128.7
22	17.3	29.4	21.9	78.4	51.8	208.2	48	8.8	17.9	9.5	51.2	17.3	125.9
23	16.0	27.6	21.3	77.2	50.2	204.6	49	8.7	17.6	9.1	50.3	16.2	123.2
24	14.8	26.1	20.8	76.1	48.7	201.1	50	8.5	17.4	8.7	49.3	15.2	120.4
25	13.8	24.7	20.3	74.9	47.2	197.6	51	8.3	17.1	8.3	48.4	14.3	117.8
26	13.0	23.7	19.8	73.8	45.7	194.2	52	8.1	16.9	7.9	47.5	13.3	115.1
27	12.4	22.8	19.3	72.7	44.2	190.8	53	8.0	16.6	7.5	46.6	12.4	112.5
28	11.9	22.1	18.7	71.6	42.7	187.4	54	7.8	16.4	7.1	45.7	11.5	109.9
29	11.5	21.6	18.2	70.5	41.2	184.0	55	7.6	16.1	6.8	44.9	10.6	107.3
30	11.3	21.3	17.7	69.4	39.8	180.7	56	7.5	15.9	6.4	44.0	9.8	104.7
31	11.1	21.0	17.2	68.3	38.4	177.4	57	7.3	15.6	6.1	43.1	9.0	102.2
32	10.9	20.8	16.7	67.2	37.0	174.1	58	7.1	15.4	5.7	42.3	8.2	99.8
33	10.8	20.6	16.2	66.2	35.6	170.9	59	7.0	15.2	5.4	41.4	7.5	97.3
34	10.7	20.5	15.8	65.1	34.2	167.7	60	6.8	15.0	5.1	40.6	6.8	94.9
35	10.7	20.4	15.3	64.1	32.9	164.5	61	6.7	14.8	4.7	39.8	6.1	92.5
36	10.6	20.3	14.8	63.0	31.5	161.3	62	6.6	14.6	4.4	39.0	5.4	90.1
37	10.5	20.2	14.3	62.0	30.2	158.2	63	6.4	14.4	4.1	38.1	4.8	87.8
38	10.3	20.0	13.9	61.0	28.9	155.1	64	6.3	14.2	3.8	37.3	4.2	85.5
39	10.2	19.8	13.4	60.0	27.7	152.1	65	6.2	14.0	3.6	36.5	3.7	83.3
40	10.1	19.6	12.9	58.9	26.4	149.0	66	6.1	13.9	3.3	35.8	3.2	81.0
41	10.0	19.5	12.5	57.9	25.2	146.0	67	6.0	13.8	3.0	35.0	2.7	78.8
42	9.8	19.3	12.0	57.0	24.0	143.1	68	5.8	13.6	2.8	34.2	2.3	76.6
43	9.7	19.0	11.6	56.0	22.8	140.1	69	5.6	13.5	2.5	33.5	1.9	74.5
44	9.5	18.8	11.1	55.0	21.7	137.2	70	5.4	13.4	2.3	32.7	1.5	72.4
45	9.4	18.6	10.7	54.0	20.5	134.4							

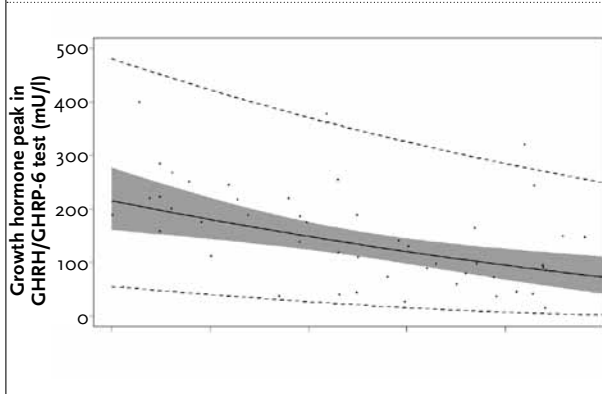**Figure 1.** *IGF-I concentrations (nmol/l)*

Black line: median. Shadow: 95% CI of mean. Dashed lines: 2.5 and 97.5 percentile.

Figure 2. *GH concentrations (mU/l) in the ITT*

Black line: median. Shadow: 95% CI of mean. Dashed lines: 2.5 and 97.5 percentile.

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Figure 3. *GH concentrations (mU/l) in the GHRH/ GHRP-6 test*

Black line: median. Shadow: 95% CI of mean. Dashed lines: 2.5 and 97.5 percentile.

There was a significant correlation between the growth hormone peak in both dynamic tests (r = 0.43, p<0.01), although the growth hormone peak in the GHRH/GHRP-6 test was significantly higher (mean 135.6 mE/l, SD 15.0) than in the ITT (mean 54.4 mE/l, SD 4.8, p<0.001) (*figure 4*). The number of days between both tests (median 12, range 1 to 112 days) did not effect the growth hormone peak.

Figure 4. *Box-and-whisker plot of the GH concentrations (mU/l) in the ITT and the GHRH/ GHRP-6 test, showing the lowest value, 25th, 50th, 75th percentile and the highest value*
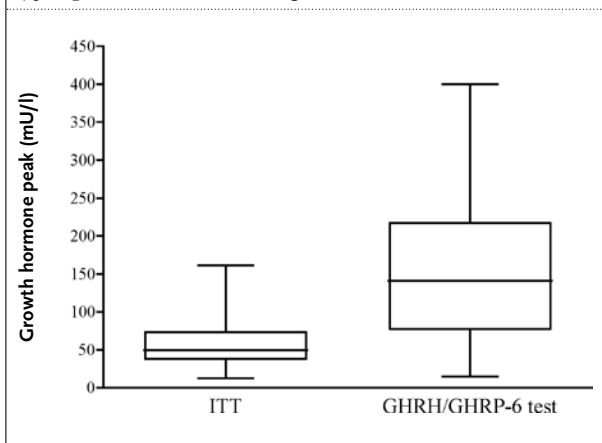
DISCUSSION

The present study provides age-adjusted reference values for plasma concentrations of IGF-I and for the GH response in the ITT and GHRH/GHRP-6 test. The recruited subjects were drawn from the general population.

We found no gender differences in IGF-I concentrations and GH response in the GHRH/GHRP-6 test. This is in line with the majority of other studies, although some found a sex difference in IGF-I concentration.[17,22-24] In our study there was an effect of gender on the GH response in the ITT, with a higher GH peak in men. This effect is small and of borderline significance. In the literature there is controversy about the effect of gender in the ITT. Some studies did not find a difference,[13,15] whereas others found a higher peak GH response in males.[25] If present at all, the differences will be negligible. Therefore, we did not establish gender-specific reference values.

The IGF-I concentration is inversely related to age in our study, which is in agreement with other studies.[22-24,26] The negative effect of BMI on the IGF-I concentration just reached significance in our study. In the literature, some other studies found an effect of BMI, although the majority did not.[24,26,27]

Age also had a negative effect on GH response in the ITT, the effect of BMI was not significant. Other studies showed a negative effect of age and BMI on the GH response.[27-29] Interesting is the effect of both of these predictors independently of each other. Biller *et al.* tested GH response in ITT in healthy subjects and found a significant inverse relationship between BMI and peak GH when controlling for age. In their study age had no significant effect. However, they only tested subjects under 55 years of age.[13] Qu *et al.* also found a negative correlation between BMI and GH response in 27 healthy subjects (age 20 to 49 years, mean BMI 24.7, range 16.0 to 32.5 kg/m²), but they did not correct for age.[15]

We found no correlation between the degree of hypoglycaemia and the peak GH response, similar to findings reported earlier by Hoeck *et al.*[25]

In the GHRH/GHRP-6 test the GH peak occurred in all subjects within 45 minutes and in most of them already after 15 or 30 minutes. This is in line with the findings of other authors.[17,19]

The peak GH response in the GHRH/GHRP-6 test was negatively associated with BMI in a multivariate analysis. A negative effect of obesity was also found by Popovic *et al.*;[17,30] they did not find a correlation with age either.[17] Micic *et al.* studied adult, aged and very old subjects (19 to 96 years) and found no difference in GH response after GHRH/GHRP-6.[31] This is also in line with the findings of Haijma *et al.*, who did GHRH/GHRP-6 tests in elderly (mean age 74, SD 1.4 years), obese (BMI 40.6, SD 1.7 kg/m²) and controls (age 51 ± 2.3, BMI 24.3 ± 1.0). They found a significant negative correlation between BMI and GH response, whereas age and GH response were not significantly correlated.[18]

Kelestimur *et al.* studied the GH peak after GHRH/ GHRP-6 in subjects with different degrees of BMI (between BMI <20 and >40 kg/m²). There was a significant

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negative effect of adiposity. In this study, there was no correction for age.[32] Several studies showed that although the GH response is lower in obese patients, the GHRH/GHRP-6 test is able to distinguish the decreased GH secretion of obesity from GHD, at least in patients with a BMI lower than 35. In patients with a BMI exceeding 35, the cut-off values should probably be adjusted.[14,18,30,32]

In our study, the peak GH response in the GHRH/GHRP-6 test and in the ITT were correlated, although the peak was significantly higher in the GHRH/GHRP-6 test. This is in agreement with other studies.[17,19] A possible explanation therefore can be that GHRP-6 acts via a receptor (ghrelin receptor) that is different from the GHRH receptor. GHRH and GHRP-6 have a synergistic action on GH release.

We found no correlation between serum IGF-I and the GH peak in the ITT (p=0.32), but a borderline significant relation between IGF-I and the GHRH/GHRP-6 test (p=0.048). Petersenn *et al.* found a significant correlation between IGF-I and both dynamic tests[19] and Popovic *et al.* found a tendency to a significant correlation between IGF-I values and GH peak in the GHRH/GHRP-6 test (p=0.051)[17]

CONCLUSION

Serum IGF-I is used as an indicator of growth hormone status, although it is well known that it is influenced by many other factors and that a normal IGF-I cannot exclude growth hormone deficiency. For that diagnosis, a provocative test of GH secretion is necessary. The ITT is considered the gold standard, but has several limitations. A good alternative is the GHRH/GHRP-6 test. In our study we have established reference values for these tests.

ACKNOWLEDGMENTS

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*In*Focus – Trombose en longembolie
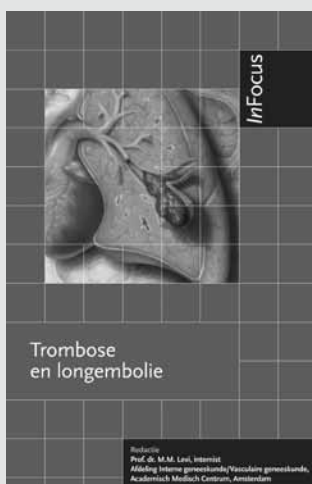
*In*Focus – Trombose en longembolie
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Diepe veneuze trombose en longembolie zijn uitingen van eenzelfde ziektebeeld, ook wel veneuze trombo-embolie genoemd. Dit is een frequent voorkomende ziekte, met een incidentie van 2 tot 3 per 1000 inwoners per jaar. Dit getal stijgt met de leeftijd, hetgeen mede wordt veroorzaakt door de hogere prevalentie van bekende risicofactoren voor veneuze trombo-embolie in de oudere populatie, zoals maligniteit, immobilisatie, chirurgie en trauma. Trombose en longembolie zijn veel voorkomende aandoeningen die spontaan kunnen optreden of het klinisch beloop van andere ziekten kunnen compliceren. Hoewel veneuze trombo-embolie goed te behandelen is met antistollingstherapie, is het een ziekte met een hoge morbiditeit. Het risico op recidiverende trombose bedraagt circa 30% na acht jaar. Longembolieën kunnen worden gecompliceerd door chronische pulmonale hypertensie. De incidentie hiervan ligt rond 4% na twee jaar. Ten slotte is de mortaliteit ten gevolge van een longembolie nog altijd aanzienlijk. Deze bedraagt ongeveer 10%.

De laatste jaren is steeds meer verbetering gekomen in de diagnostische aanpak en het therapeutisch management van zowel veneuze als arteriële trombo-embolie. Een belangrijke rol is daarbij weggelegd voor nieuwe vormen van diagnostiek, maar met name ook voor steeds betere behandelmethoden.

In dit boekje wordt een praktische handleiding gegeven voor de diagnostiek en behandeling van trombo-embolische aandoeningen volgens de nieuwste inzichten.

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