CLINICAL STUDY

Exercise-induced GH secretion in the assessment of GH deficiency in adult individuals

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Abstract

Objective: The role of exercise testing in the assessment of GH deficiency (GHD) in adult patients is currently unclear. This study aimed at evaluating the diagnostic value of exercise-induced GH levels in the detection of severe GHD in adult patients.

Methods: Fourteen patients confirmed to have severe GHD according to current guidelines and 20 healthy control individuals (CI) exercised for 120 min at 50–60% of their individual $\text{VO}_{2\text{max}}$. GH was measured before and every 30 min throughout exercise. The diagnostic value of predicting GHD was assessed by performing receiver operating characteristics (ROC) analysis for each time point of GH assessment. To optimise comparability within the study population a sub-analysis with ten individuals specifically matched for gender, age, body mass index and waist was performed.

Results: Exercise-induced GH secretion was significantly lower in patients with GHD than in CI ($P < 0.001$). Area under the ROC curve (AUC_{ROC}) was 0.954 ± 0.033 , 0.993 ± 0.009 , 0.989 ± 0.012 and 0.992 ± 0.009 for the overall population and 0.870 ± 0.086 , 0.980 ± 0.024 , 0.970 ± 0.034 and 0.978 ± 0.027 for the matched individuals at 30, 60, 90 and 120 min of exercise respectively. At 60 min of exercise a cut off GH value of 2.4 ng/ml translates into a sensitivity of 100% and a specificity of 95 and 90% in the diagnosis of GHD for the overall population and matched individuals respectively.

Conclusion: GH assessment during a standardised aerobic exercise of moderate intensity is a reliable test with high diagnostic accuracy in predicting severe GHD in adult individuals. Based on the current findings exercise duration of 60 min appears to be sufficient for diagnostic purposes.

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Introduction

Little is known regarding the value of exercise testing in the diagnosis of severe GH deficiency (GHD) in adult patients. While more extensive data is available for children and adolescents (1), studies assessing the reliability of exercise testing in the diagnosis of GHD in these patients have revealed controversial findings (2–5). Several reports suggested a role for exercise testing in screening settings exclusively (2–4). Other more recent reports in children entirely questioned the reliability of GH testing during or after exercise (5). Such discrepancies may at least partly be due to differences in study populations, as well as the intensity and duration of exercise in the various protocols (3, 4, 6). Moreover, the time point of GH measurement during or after exercise may strongly affect results. We (7) and others (8–10) have reported GH to reach peak values between 30 and 45 min after start of exercise in adult individuals.

Investigations in healthy adults suggest exercise to compare favourably with well-accepted stimulation

tests of GH secretion (10). However, to the best of our knowledge an investigation of exercise-induced GH secretion in the diagnosis of adult patients with GHD has not been performed so far. This study aimed at prospectively assessing the diagnostic value of an aerobic exercise intervention in the evaluation of severe GHD in adult patients. Measurements of GH at different time points were performed to assess potential time-dependency in diagnostic accuracy.

Materials and methods

This was a prospective single-centre open case-control study performed at the Endocrine Division of the University Hospital of Bern, Switzerland. The study followed the Declaration of Helsinki, the guidelines of good clinical practice, the Swiss health laws and the ordinance on clinical research. Each participant gave informed written consent, and the study was approved by the local ethics committee in Bern, Switzerland. The study population encompassed 14 patients with severe

GHD and 20 control individuals (CI). Severe GHD was defined according to the current guidelines either based on an increase of GH to <5.1 ng/ml during an insulin tolerance test (ITT) with a nadir plasma glucose of <2.2 mmol/l and hypoglycaemic symptoms, or an insufficient GH releasing hormone (GHRH)/arginine test with body mass index (BMI)-dependent cut offs (11.5, 8.0 and 4.2 ng/ml for BMI <25 , 25–30 and >30 kg/m² respectively), or insufficiency of at least three pituitary axes in addition to a low value for insulin-like growth factor 1 (IGF1) (11–13). Owing to a potential interference of oral oestrogens with IGF1 levels the diagnosis of GHD in female patients was based on stimulation testing, exclusively. Patients had to be under stable conventional hormone replacement therapy as needed for at least 6 months. Exclusion criteria were ACTH- or GH-secreting pituitary adenoma, abnormal liver or renal function, active neoplasia, severe cardiovascular disease, heart failure NYHA III and IV, diabetes mellitus or inability to exercise. To optimise comparability within the study population, 10 of the 14 GHD patients and 10 of the 20 CI were specifically matched for gender, age, BMI and waist. Waist circumference was measured in upright position with a flexible tape placed on a horizontal plane at the level of the iliac crest at the end of a normal expiration. Before the study a stepwise incremental exercise test was performed to assess peak aerobic capacity using breath-by-breath analysis (Oxycon alpha, Jaeger, Wurzburg, Germany). GHD patients and CI attended the hospital after an overnight fast. GH values were assessed immediately before start of the exercise and then every 30 min. Patients and CI exercised on a treadmill for 2 h at an intensity of 50–60% of $\text{VO}_{2\text{max}}$. Serum GH concentrations were

determined with an enzymatically amplified, two-step sandwich immunoassay (Diagnostic System Laboratories, Webster, TX, USA). The inter-assay coefficient of variation (CV) was 6.5% and the intra-assay CV was 4.3%. Results are expressed as mean $\pm$ S.E.M., unless otherwise specified. The area under the curve (AUC) was calculated using cubic splines. After checking for normal distribution parameters were compared by unpaired *t*-tests. The diagnostic value in predicting GHD was calculated for each time point of GH assessment during exercise by performing receiver operating characteristics (ROC) analysis. In a ROC analysis, the diagnostic test under investigation (for the present analysis: exercise-induced GH concentrations) is compared with an accepted gold standard (for the present analysis: GHD assessed according to guidelines (11–13)). First, ROC analysis was performed including all GHD patients and all CI. In a sensitivity analysis with optimised comparability we then restricted the analysis on the ten GHD patients and the ten CI matched for gender, age, BMI and waist circumference. All statistical analyses were done with Stata 10.1 (Stata Corp., College Station, TX, USA).

Results

Fourteen GHD patients (nine male/five female) and 20 CI (14 male/six female) were included into the study. GHD was due to pituitary or hypothalamic disease in all cases, individual clinical characteristics of the GHD patients are summarised in Table 1. GHD patients had a significantly lower IGF1 compared with CI (66.0 ± 14.4 vs 143.0 ± 11.4 ng/ml, $P < 0.001$). While waist circumference was similar in GHD and CI (90.8 ± 3.0 and

Table 1 Characteristics of patients presenting with GHD.

Age (years)	Gender (M/F)	Diagnosis	Treatment	Dur. HP (years)	Hormone deficiencies	Dx GHD	IGF1 (ng/ml)
46	M	HIPA	Surgery DxRT	8	GH*, ACTH, TSH and LH/FSH	Three axes	72
45	M	HIPA	Surgery DxRT	29	GH*, ACTH, TSH and LH/FSH	Three axes	33
55	F	Epidermoid cyst	Surgery	8	GH*, ACTH and LH/FSH	ITT	66
54	M	Gonadotroph cell adenoma	Surgery	1	GH* and LH/FSH*	ITT	88
18	F	Idiopathic GHD		17	GH* and LH/FSH	ITT	41
48	M	HIPA	Surgery	1	GH*, ACTH, TSH and LH/FSH	Three axes	40
31	M	Prolactinoma	DA	3	GH*, ACTH, TSH and LH/FSH	Three axes	87
57	F	HIPA	Surgery	1	GH*, TSH and LH/FSH	ITT	69
32	M	Prolactinoma	DA	1	GH* and LH/FSH	ITT	102
40	F	HIPA	Surgery	1	GH*	GHRH Arg.	69
67	M	Prolactinoma	Surgery	33	GH*, ACTH, TSH, LH/FSH and ADH	ITT	92
66	M	HIPA	Surgery	3	GH*, ACTH, TSH and LH/FSH	Three axes	65
50	F	Prolactinoma	Surgery	19	GH*, ACTH, TSH and LH/FSH	ITT	65
69	M	Gonadotroph cell adenoma	Surgery	3	GH*, ACTH, TSH and LH/FSH	Three axes	34

Dur. HP, Duration of hypopituitarism; Dx GHD, underlying diagnostic criteria for GH deficiency; HIPA, hormone-inactive pituitary adenoma; DxTR, pituitary radiotherapy; DA, dopamine agonist; ADH, antidiuretic hormone; ITT, insulin tolerance test; GHRH Arg., GH releasing hormone + arginine stimulation test; three axes, deficiency of at least three pituitary axes in combination with low IGF1. Hormone deficiencies marked with an asterisk (*) have not been substituted for at least the past 6 months before the test. All the other hormone deficiencies have been replaced as needed for at least 6 months.

Table 2 Clinical characteristics of GHD patients and control individuals. Results are mean $\pm$ S.E.M.

	All individuals			Matched individuals		
	GHD	CI	P values	GHD	CI	P values
Male/female	9/5	14/6		6/4	6/4	
Age (years)	48.4 (± 4.0)	36.9 (± 2.9)	0.02	42.5 (± 4.0)	42.9 (± 4.0)	0.95
BMI (kg/m ²)	27.0 (± 1.1)	23.6 (± 0.9)	0.03	26.6 (± 1.2)	25.3 (± 1.7)	0.53
Waist (cm)	90.8 (± 3.0)	85.2 (± 3.7)	0.27	89.3 (± 4.1)	90.7 (± 6.0)	0.85
VO _{2max} (ml/min $\times$ kg)	35.6 (± 1.8)	51.9 (± 2.8)	<0.001	35.5 (± 2.3)	41.5 (± 1.7)	0.05
IGF1 (ng/ml)	66.0 (± 14.4)	143.0 (± 11.3)	<0.001	66.6 (± 7.3)	117.1 (± 9.7)	<0.001

GHD, GH deficient patients; CI, control individuals; Waist, waist circumference; VO_{2max}, maximal oxygen uptake. Bold P values, statistically significant.

85.2 $\pm$ 3.7 cm), the two groups differed in age (48.4 $\pm$ 4.0 and 36.9 $\pm$ 2.9 years, $P=0.02$), BMI (27.0 $\pm$ 1.1 and 23.6 $\pm$ 0.9 kg/m², $P=0.03$) and VO_{2max} (35.6 $\pm$ 1.8 and 51.9 $\pm$ 2.8 ml O₂/kg body weight per min, $P<0.001$; Table 2). Age, BMI, waist circumference and VO_{2max} did not differ between the ten matched GHD and the ten matched CI individuals (Table 2).

Figure 1 shows GH levels before and throughout exercise separately for all participants (panel A), and for the matched individuals (panel B). Mean GH levels were lower in GHD patients before exercise in the overall population (0.43 $\pm$ 0.25 vs 3.7 $\pm$ 1.2 ng/ml, $P=0.03$) and a similar pattern was found in the matched individuals (0.6 $\pm$ 0.3 vs 2.2 $\pm$ 1.1 ng/ml, $P=0.19$). During exercise there were significantly lower mean GH concentrations in GHD patients compared with CI in both the overall population (AUC 79.6 $\pm$ 22.78 vs 1237.6 $\pm$ 154.3 ng $\times$ min/ml, $P<0.001$) and in the matched individuals (AUC 100 $\pm$ 29.5 vs 926.8 $\pm$ 196.9 ng $\times$ min/ml, $P<0.001$). Mean peak GH levels were significantly lower in GHD than in CI in the overall population (1.1 $\pm$ 0.4 vs 13.4 $\pm$ 1.8 ng/ml, $P<0.001$) and the matched individuals (1.5 $\pm$ 0.5 vs 11.6 $\pm$ 3.2 ng/ml, $P=0.006$).

Figure 2 displays ROC curves for different time points throughout exercise, based on data from all individuals. Area under the ROC curve (AUC_{ROC}) was 0.954 $\pm$ 0.033, 0.993 $\pm$ 0.009, 0.989 $\pm$ 0.012 and 0.992 $\pm$ 0.009 at 30, 60, 90 and 120 min of exercise respectively. Although AUC_{ROC} did not significantly differ according to time point, the highest value tended to result at 60 min.

A similar pattern resulted when ROC analyses were restricted to the 20 individuals matched for age, gender, BMI and waist (Fig. 3). AUC_{ROC} was 0.870 $\pm$ 0.086, 0.980 $\pm$ 0.024, 0.970 $\pm$ 0.034 and 0.978 $\pm$ 0.027 at 30, 60, 90 and 120 min of exercise respectively. Again, AUC_{ROC} did not significantly differ according to time point, but the highest value tended to result at 60 min.

Table 3 gives an overview of sensitivity and specificity of different GH levels at various time points for all individuals and restricted to the matched individuals. Based on the results of the overall population, a GH cut off value of 1.0 ng/ml at 60 min translates into a specificity of 100% and a sensitivity of 85.7% in the

diagnosis of GHD, whereas a cut off level of 2.4 ng/ml results into a sensitivity of 100% and a specificity of 95%. This corresponds to a correct classification of 94.1 and 97.1% respectively.

Discussion

This study prospectively assessed the diagnostic accuracy of exercise-induced GH in the assessment of severe GHD in adult patients. During a standardised aerobic exercise we found that GH concentrations revealed a high diagnostic accuracy with AUC_{ROC} ranging from 0.95 to 0.99 for different time points. While differences between time points were small and did not reach conventional levels of statistical significance the highest value for the AUC tended to result at 60 min of exercise. GH levels taken at this time point translated into a correct classification of individuals in 94–97% of cases, depending on the chosen cut off levels. Restricting our analyses to a sub-group of individuals (GHD and CI) matched for age, gender, BMI and waist, resulted in very comparable results with AUC_{ROC} between 0.87 and 0.98, confirming the robustness of these findings.

To the best of our knowledge, this is the first study in adult patients directly comparing the value of exercise testing with current diagnostic guidelines of severe GHD. Earlier studies performed in children or adolescents have questioned the value of exercise as a diagnostic test in GHD (5) or have limited its applicability to screening purposes (2–4). The high sensitivity established in this study corroborates the

Figure 1 Mean $\pm$ S.E.M. GH concentrations during exercise for GHD patients (open triangles) and control individuals (closed squares). Left panel (A) depicts results for all individuals, right panel (B) depicts results for matched individuals, exclusively.

Figure 2 ROC curves for GHD according to different time points of exercise based on all individuals; after 30 min (panel A); after 60 min (panel B); after 90 min (panel C) and after 120 min (panel D).

value of exercise testing in the screening of GHD and extends these findings to adult patients. In clinical practice, however, there may be a greater value in confirming the diagnosis and avoiding false positive tests. The present analysis suggests that exercise-induced GH may provide a test with a high specificity thereby supporting its use in the confirmation of suspected severe GHD in adult individuals. We acknowledge that the predictive value of a test generally depends on the prevalence of a disease in the population under investigation (14). A prevalence of 0.02% for GHD in a general adult population (15) thereby translates into a positive predictive value (PPV) of only 0.4% if GH is measured at 60 min (cut off level 2.4 ng/ml). However, the pretest probability may be considerably higher in a population under investigation for potential GHD at a tertiary referral centre. Assuming a prevalence of 30% increases PPV to 89.6% if GH is measured after 60 min of aerobic exercise. Decreasing the cut off level of GH to 1 ng/ml further increases specificity as well as PPV to 100%.

The discrepant findings regarding diagnostic accuracy between this study and earlier reports may have several reasons. First, the accuracy of a diagnostic test may differ according to the individuals under investigation. As previous diagnostic studies were essentially limited to children or adolescents the use of invasive testing with ITT had to be restricted (2, 3, 16). Furthermore, it is well understandable that the duration of exercise was limited by the young age of the participants (2). Secondly, the studies differed considerably regarding the applied exercise protocols. Since the duration and intensity of exercise strongly affect GH secretion (8, 9), this is likely to have influenced diagnostic values. Interestingly, peak GH levels found in control individuals in this study were comparable to earlier studies with similar exercise intensity (7, 10). Of note, a linear dose-relationship between exercise intensity and GH secretory response has been suggested in young healthy men (9). Previous

reports indicate that an aerobic exercise duration of at least 20–30 min is required to provoke a relevant GH secretion, whereas a shorter exercise duration may result in comparably high or even higher GH levels if exercise is performed above the aerobic threshold (7, 8, 10, 17). This implies that a certain intensity of exercise may be required over time to optimise diagnostic accuracy (e.g. the concept of a time–intensity product). Finally, the time point of GH measurement varied between studies, further limiting direct comparability with the present analysis (2, 6). In this study, GH values at 30 min of exercise tended to be associated with slightly smaller AUC_{ROC} , whereas results were nearly identical for 60, 90 and 120 min respectively. Based on these findings it may be sufficient to limit aerobic exercise to duration of 60 min. Whether a shorter exercise with higher intensity may result in comparable diagnostic accuracy is currently speculative.

GH replacement has been shown to have beneficial effects with regard to quality of life as well as physiological and metabolic parameters (18). Reliable tests for GHD are, therefore, important to identify individuals that may potentially benefit from GH substitution. We acknowledge that the currently available test protocols including the ITT or the GHRH arginine test are established as reliable tools in assessing the integrity of the GH axis. However, an advantage of exercise testing compared with pharmacological stimulation tests may be the endogenous and, therefore, perhaps more physiological stimulation of GH secretion (10, 16). We are aware that exercise testing over 60 min or even longer may not be feasible in every patient in clinical practice. Of note, in this study every single participant successfully finished the exercise test, thereby at least partially corroborating the feasibility of exercise testing in adults. Conversely, we fully acknowledge that the participants in our study were comparably

Figure 3 ROC curves for GHD according to different time points of exercise based on the 20 matched individuals; after 30 min (panel A); after 60 min (panel B); after 90 min (panel C) and after 120 min (panel D).

Table 3 Overview of sensitivity and specificity. Note that sensitivity and specificity of exercise-induced GH levels are calculated according to different cut off values of exercise-induced GH. The calculation is based on the results of the receiver operating characteristics analysis comparing exercise-induced GH values with current diagnostic guidelines of adult GHD (see Figs 2 and 3).

Time point (min)	Cut off GH level (ng/ml)	Sensitivity (%)	Specificity (%)	Correctly classified (%)
All individuals				
30	≤ 4.4	100	85	91.1
	≤ 0.3	50	100	79.4
60	≤ 2.4	100	95	97.1
	≤ 1.0	85.7	100	94.1
90	≤ 1.3	100	95	97.1
	≤ 0.6	78.6	100	91.2
120	≤ 1.1	100	95	97.0
	≤ 0.5	84.6	100	93.9
Matched individuals				
30	≤ 4.4	100	70	85
	≤ 0.2	30	100	65
60	≤ 2.4	100	90	95
	≤ 1.0	80	100	90
90	≤ 1.3	100	90	95
	≤ 0.5	70	100	85
120	≤ 1.1	100	90	94.7
	≤ 0.5	77.8	100	89.5

young. Therefore, results do not unrestrictedly apply to older individuals or patients with cardiopulmonary disease. Furthermore, this study should be taken as a proof of principle, extending the findings in paediatric GHD patients to adult individuals. Further studies will have to investigate whether exercise of a shorter duration and higher intensity results in similarly high diagnostic accuracy.

The strength of this study lies in its prospective design with repetitive GH measurements over an extended duration of standardised aerobic exercise as well as its comparison with GHD defined according to current guidelines. Of note, CI were younger and less obese than GHD in the overall study population, and this fact may have led to an overestimation of the discriminatory power of exercise testing. However, the findings in the overall study population were reproduced in a sensitivity analysis restricted on GHD patients and CI specifically matched for age, gender, BMI and waist circumference and AUCs_{ROC} were similar in both groups. We acknowledge that the sample size was comparably small and although every participant accomplished the exercise test a selection bias cannot be fully ruled out. The study was limited to patients with severe GHD, and no conclusions regarding more subtle forms of GHD should be drawn. Of note is that in many countries, the indication for GH replacement is restricted to patients with severe GHD. Finally, although GH concentrations were measured at multiple time points throughout exercise the sampling interval of 30 min restricts statements on the optimal time point of GH measurement.

In conclusion, GH values obtained during a standardised aerobic exercise of moderate intensity revealed a high diagnostic accuracy in predicting severe GHD in adult individuals. Based on the present findings exercise duration of 60 min appears to be sufficient for diagnostic purposes. Whether a shorter exercise on higher intensity may lead to comparable results has to be assessed in future studies.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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