Growth Hormone & IGF Research 29 (2016) 39–44

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Regulation of fuel metabolism during exercise in hypopituitarism with growth hormone-deficiency (GHD)

Thomas Zueger [a,1], Hannah Loher [a,1], Andrea Egger [b], Chris Boesch [c], Emanuel Christ [a,*]

[a] Division of Endocrinology, Diabetes and Clinical Nutrition, Inselspital, Bern University Hospital and University of Bern, Switzerland
[b] Department of Internal Medicine, University Hospital of Basel, CH-4056 Basel, Switzerland
[c] Department of Clinical Research & Institute of Interventional, Diagnostic and Pediatric Radiology, University of Bern, Bern, Switzerland

ARTICLE INFO

Article history:
Received 13 January 2016
Received in revised form 7 March 2016
Accepted 25 March 2016
Available online 13 April 2016

Keywords:
Growth hormone deficiency
Exercise
Endurance capacity
Fuel metabolism
Lipolysis

ABSTRACT

Objective: Growth hormone (GH) has a strong lipolytic action and its secretion is increased during exercise. Data on fuel metabolism and its hormonal regulation during prolonged exercise in patients with growth hormone deficiency (GHD) is scarce. This study aimed at evaluating the hormonal and metabolic response during aerobic exercise in GHD patients.

Design: Ten patients with confirmed GHD and 10 healthy control individuals (CI) matched for age, sex, BMI, and waist performed a spiroergometric test to determine exercise capacity (VO_{2max}). Throughout a subsequent 120-minute exercise on an ergometer at 50% of individual VO_{2max} free fatty acids (FFA), glucose, GH, cortisol, catecholamines and insulin were measured. Additionally substrate oxidation assessed by indirect calorimetry was determined at begin and end of exercise.

Results: Exercise capacity was lower in GHD compared to CI (VO_{2max} 35.5 ± 7.4 vs 41.5 ± 5.5 ml/min * kg, $p = 0.05$). GH area under the curve (AUC-GH), peak-GH and peak-FFA were lower in GHD patients during exercise compared to CI (AUC-GH 100 ± 93.2 vs 908.6 ± 623.7 ng * min/ml, $p < 0.001$; peak-GH 1.5 ± 1.53 vs 12.57 ± 9.36 ng/ml, $p < 0.001$, peak-FFA 1.01 ± 0.43 vs 1.51 ± 0.56 mmol/l, $p = 0.036$, respectively). There were no significant differences for insulin, cortisol, catecholamines and glucose. Fat oxidation at the end of exercise was higher in CI compared to GHD patients (295.7 ± 73.9 vs 187.82 ± 103.8 kcal/h, $p = 0.025$).

Conclusion: A reduced availability of FFA during a 2-hour aerobic exercise and a reduced fat oxidation at the end of exercise may contribute to the decreased exercise capacity in GHD patients. Catecholamines and cortisol do not compensate for the lack of the lipolytic action of GH in patients with GHD.

1. Introduction

Hypopituitary patients with growth hormone deficiency (GHD) tend to have a reduced aerobic exercise capacity compared with sedentary control subjects [7,18].

It is established that the lack of growth hormone (GH) is accompanied by a decreased lean body mass [6,14,27] and reduced performance of the cardiovascular system [7,8]. Moreover GHD impairs the oxygen transport capacity [3]. All these factors may contribute to a reduced exercise capacity.

In healthy subjects exercise induces a strong GH secretion [17]. In patients suffering from GHD such an exercise induced GH-response is lacking [31,32]. Since GH is known to have a strong lipolytic effect [23] we speculate that lipolysis may also be reduced during exercise in patients with GHD compared to healthy individuals. This effect could either be compensated by an increased secretion of alternative lipolytic hormones or by changes in fuel metabolism towards an increased oxidation of carbohydrates. We, therefore, aimed at investigating the hormonal and metabolic response during exercise in GHD patients compared to matched control subject. We hypothesized that a decreased availability of free fatty acids (FFA) and possibly a reduced fat oxidation during exercise may contribute to the reduced exercise capacity in patients with GHD.

2. Material & methods

This was a prospective single-center open case-control study performed at the University Hospital of Bern, Switzerland. All investigations were carried out at the Division of Endocrinology, Diabetes and Clinical Nutrition. The study was approved by the local review board

Abbreviations: ACTH, adrenocorticotropic hormone; AUC, area under the curve; BMI, body mass index; CI, control individuals; CV, coefficient of variation; FFA, free fatty acids; GH, growth hormone; GHD, growth hormone deficiency; GHRH, growth hormone releasing hormone; RER, respiratory exchange ratio; VCO_2, carbon dioxide output; VO_2, oxygen uptake; VO_{2max}, maximum oxygen uptake capacity.

* Corresponding author at: Division of Endocrinology, Diabetes and Clinical Nutrition, Inselspital, Bern University Hospital and University of Bern, CH-3010 Bern, Switzerland.
E-mail address: emanuel.christ@insel.ch (E. Christ).

[1] T. Zueger and H. Loher have equally contributed to this manuscript.

http://dx.doi.org/10.1016/j.ghir.2016.03.007
1096-6374/

(Kantonale Ethikkommission, Bern) and all subjects gave written informed consent. The study was performed according to the declaration of Helsinki, the guidelines of good clinical practice, and the Swiss health laws on clinical research (Clinical.Trials.gov: NCT00491582).

2.1. Participants

The study population encompassed 10 patients with severe GHD and 10 sedentary control individuals (CI) matched for gender, age, body mass index (BMI) and waist circumference. 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 hypoglycemic symptoms, a pathological 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/m^2 respectively), or insufficiency of at least three pituitary axes in addition to a low value for insulin-like growth factor 1 (IGF-1) [5,21,22]. Owing to a potential interference of oral estrogens with IGF-1 levels the diagnosis of GHD in female patients was based on stimulation testing, exclusively.

Patients were included provided they had been under stable conventional hormone replacement therapy (glucocorticoids, thyroxin and sex hormones) as needed for at least 6 months and capable to exercise on a treadmill for 2 h. Exclusion criteria were (former or present) ACTH- or GH-secreting pituitary adenoma, abnormal liver or renal function, active neoplasia, severe cardiovascular disease (unstable coronary artery disease, heart failure New York Heart Association III–IV), diabetes mellitus, hemophilia, therapy with drugs known to affect lipid or glucose metabolism or inability to exercise.

2.2. Determination of baseline characteristics and VO_{2max}

Participants attended the endocrine investigation unit after having fasted for at least 4 hours. All volunteers had restrained from physical activity for 72 h before the test. Body weight was measured on an electronic balance with subjects wearing light clothes and no shoes. Height was assessed by a stadiometer. BMI was calculated as the weight divided by the square of the height. End-expiratory waist circumference was measured with a flexible tape placed on a horizontal plane at the level of the iliac crest. Lean body mass was assessed by MRI as previously described [1]. Maximal aerobic exercise capacity was determined during an incremental workload test on a treadmill (CARDIOVIT AT-104 PC Ergo-Spirometrie, Schiller, Baar, Switzerland) until exhaustion. Increase of workload was chosen according to the estimated fitness status in order to obtain an exercise time of about 9–12 min. During the test expired oxygen, carbon dioxide content and minute ventilation were measured continuously (Oxycon alpha, Jaeger, Würzburg, Germany). Furthermore, blood pressure was measured every two minutes and subjective level of exhaustion was assessed with the Borg scale. Fifty % of the heart rate at maximal aerobic exercise was calculated and the corresponding workload was chosen. After the maximal exercise test and a short break, the subjects were jogging for 30–60 min on the treadmill. This exercise aimed at determining the velocity and gradient of the treadmill at which the subject exhibited a heart rate that corresponded to 50% of the heart rate at maximal oxygen consumption (VO_{2max}).

2.3. Two hour physical exercise on a treadmill at 50% of VO_{2max}

GHD patients and CI attended the hospital after an overnight fast. Upon arrival, they received a standardized light meal. Hydrocortisone replacement therapy was administered as needed. Patients and CI exercised on a treadmill for 2 h at an intensity of 50% of VO_{2max}. Glucose, free fatty acid, insulin, cortisol, GH, norepinephrine and epinephrine values were assessed immediately before start of the exercise and then every 30 min. Furthermore, spirometric parameters (VO_2, VCO_2 and RER) were measured during the first and last 15-minute of exercise (Oxycon alpha, Jaeger, Würzburg, Germany). Fat and carbohydrate oxidation were calculated based on Consolazio et al. [4].

2.4. Biochemical analysis

Blood glucose levels were measured by a glucose-oxidase method using YSI2300 (Yellow Springs Instruments, Yellow Springs, OH, USA). Insulin concentrations were measured with electro-chemiluminescence immunoassays (Roche Modular-E170; Roche Diagnostics, Rotkreuz, Switzerland). The intra-assay CV was 1.1% and the inter-assay CV was 3.6%. Cortisol concentrations were measured with electro-chemiluminescence immunoassays (Roche Modular-E170; Roche Diagnostics, Rotkreuz, Switzerland). The intra-assay CV was 1.7% and the inter-assay CV was 2.2%. FFA concentrations were determined using a commercially available kit (Wako Pure Chemical, VWR International, Dietikon, Switzerland). The intra-assay CV was 1.5% and the inter-assay CV was 15%. Serum GH concentrations were determined with an enzymatically amplified, two-step sandwich immunoassay (Diagnostic System Laboratories, Webster, TX, USA; The interassay CV was 6.5% and the intraassay CV 4.3%). Plasma catecholamines (norepinephrine and epinephrine) were analyzed using HPLC with amperometric detection (modified method of the RECIPE kit (ClinRep®, RECIPE Chemicals and Instruments GmbH, Munich, Germany)) [13].

2.5. Statistical analysis

Results are expressed as mean ± standard deviation (SD), unless otherwise specified. The area under the curve (AUC) was calculated using cubic splines. Incremental AUC was determined using the delta values between the nadir and remaining measurements of every individual. Continuous variables were analyzed for normal distribution using Shapiro–Wilk test and qq-plots. Parametric variables were compared using t-tests and repeated measure analysis of variance. Non-parametric variables were analyzed using Wilcoxon rank sum and Wilcoxon signed rank tests or Friedman tests. Within group comparison was performed by paired tests, whereas between group analysis was performed by unpaired tests. In case of multiple comparison postestimation procedure applying a Bonferroni or Dunn's correction was used. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed with Stata version 12.1 (Stata Corp., College Station, TX) and GraphPad Prism version 6.0 (GraphPad Software, La Jolla, California, USA).

3. Results

3.1. Participants' characteristics

Ten GHD patients (6 male/4 female) and ten sedentary CI matched for gender, age, BMI and waist circumference were included into the study. Among the ten GHD individuals substitution of corticotropic, gonadotropic and thyreotropic axis was necessary in five, eight and five patients, respectively. GHD patients had significantly lower IGF-1 levels compared to CI (66.6 ± 22.9 ng/ml vs 117.1 ± 30.5 ng/ml, $p < 0.001$) and had a reduced exercise capacity compared to CI assessed by VO_{2max} (35.5 ± 7.4 ml/min * kg vs 41.5 ± 5.5 ml/min * kg, $p = 0.05$). Additional clinical characteristics are summarized in Table 1.

3.2. Metabolites

Metabolic response during exercise is summarized in Table 2. In patients with GHD Glucose concentrations were stable throughout the exercise (ANOVA $p = 0.52$), whereas FFA showed a significant increase during exercise with peak level at 120 min ($p < 0.001$; see Fig. 1a & b). In CI Glucose concentrations were stable throughout the exercise (ANOVA $p = 0.32$) but FFA concentrations showed a more pronounced increase