Metabolic Responsiveness to Growth Hormone in Children

Thesis

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Examiner:
Professor Jan-Marten Wit
Leiden University, The Netherlands

The thesis is based on the following papers:

I. **Ralph Decker, Kerstin Albertsson-Wikland, Berit Kriström, Andreas F. M. Nierop, Jan Gustafsson, Ingvar Bosaeus, Hans Fors, Ze'ev Hochberg, Jovanna Dahlgren**
"Metabolic outcome of GH treatment in prepubertal short children with and without classical GH deficiency" *Clinical Endocrinology (Oxf.) 2010;73:346–354.*

II. **Ralph Decker, Kerstin Albertsson-Wikland, Berit Kriström, Maria Halldin, Jovanna Dahlgren**
"Decreased GH dose after the catch-up growth period maintains metabolic outcome in short prepubertal children with and without classic GH deficiency"
(resubmitted to Clinical Endocrinology)

III. **Björn Andersson, Ralph Decker, Andreas F. M. Nierop, Ingvar Bosaeus, Kerstin Albertsson-Wikland, Gunnel Hellgren**
"Protein profiling identified dissociations between growth hormone-mediated longitudinal growth and bone mineralization in short prepubertal children"
Journal of Proteomics 2011*;74:89–100.*

IV. **Ralph Decker, Björn Andersson, Andreas F. M. Nierop, Ingvar Bosaeus, Jovanna Dahlgren, Kerstin Albertsson-Wikland, Gunnel Hellgren**
"Protein markers predict body composition during growth hormone (GH) treatment in short prepubertal children" *(manuscript)*

V. **Ralph Decker, Anders Nygren, Kerstin Albertsson-Wikland, Berit Kriström, Andreas F. M. Nierop, Jan Gustafsson, and Jovanna Dahlgren**
"Different thresholds of tissue-specific dose-responses to growth hormone in short prepubertal children" *(submitted to BMC Medical Informatics and Decision Making)*

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ABSTRACT

Metabolic effects of growth hormone (GH) therapy in short children have not been clearly established owing to the previous lack of controlled trials studying the metabolic outcome in response to different GH doses despite the known effects of GH on insulin sensitivity, lipid profile, and body composition. It has previously been shown that individualized GH doses during catch-up growth significantly reduce the proportion of unexpectedly good and poor responders around a predefined individual growth target in short prepubertal children. In the research on which this thesis is based, 87 prepubertal children were treated with six different GH doses, individually chosen according to a prediction model of GH sensitivity regarding linear bone growth.

The first hypothesis was that the variance of the metabolic response during individualized GH treatment would be reduced. This was confirmed: individualized GH dosing during catch-up growth reduced the variance in insulin and HOMA by 34.2 % and 38.9 %, respectively (Paper I).

This led to the second hypothesis that metabolic responsiveness to GH treatment partly parallels and partly dissociates from the longitudinal growth response. This too was confirmed: a GH dose-dependent anabolic component was identified in contrast to a dose-independent lipolytic component (Papers I and II). This finding raised the question of whether different thresholds would achieve certain metabolic effects, such as anabolic effects, lipolytic effects, and glucose metabolism.

A pharmaco-proteomic approach was introduced in order to identify previous unknown biomarkers to predict metabolic responses to GH treatment as well as to investigate the physiology of GH (Papers III and IV). These results have been published recently, showing dissociations between GH-mediated longitudinal bone growth and bone mineralization and thereby confirming the second hypothesis named above (Paper III).

The third hypothesis was that patients with and without classical GH deficiency (GHD) had correspondingly different thresholds of responsiveness to GH treatment among different metabolic functions. The data confirmed the hypothesis and, moreover, increasing effective GH doses were needed to achieve specific metabolic effects (Paper V).

This research provides further evidence of the benefits of individualized GH dosing in order to maintain metabolic functions within age-adjusted reference values and to normalize body composition. In the long term, this might minimize metabolic and cardiovascular risk factors in children suffering from GHD or reduced GH responsiveness.

Keywords: Hormonal responsiveness, metabolic outcome, growth hormone, individualized treatment, body composition, fasting insulin, leptin, prediction model, proteomics, SELDI, mass spectrometry, protein pattern, biomarkers, apolipoproteins, nutrition markers

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