Prediction Models and Pharmacogenomics in Adult Growth Hormone Deficiency

av

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Avhandlingen baseras på följande delarbeten:

I. Models to predict changes in serum IGF-I and body composition in response to GH replacement therapy in GH-deficient adults.
Barbosa EJL, Koranyi J, Filipsson H, Bengtsson B-Å, Boguszewski C, Johannsson G.

II. Influence of the exon3-deleted/full-length growth hormone (GH) receptor polymorphism on the response to GH replacement therapy in adults with severe GH deficiency.
Barbosa EJL, Palming J, Glad CAM, Filipsson H, Koranyi J, Bengtsson B-Å, Carlsson LMS, Boguszewski CL, Johannsson G.

III. Genotypes associated with lipid metabolism contribute to differences in serum lipid profile of growth hormone deficient (GHD) adults before and after GH replacement therapy.

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Abstract

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The overall aim of this thesis was to study clinical and genetic factors that influence response to growth hormone replacement therapy (GHRT) in GH deficient (GHD) adults. The patients were part of a cohort of adults with hypopituitarism and severe GHD who were studied before and after 12 months of GHRT. The dose regimen was individualized in order to attain normal IGF-I levels. Logistic regression (LR) analysis was used to identify good and poor responders to GHRT. The candidate gene approach was used to study single nucleotide polymorphisms (SNPs) in the GH receptor (GHR) gene, in genes related to GH signaling pathways, lipid metabolism and renal tubular function. Changes in IGF-I levels, body composition (BC), lipid profile and extracellular water (ECW) were analyzed as the GHRT outcomes. We identified gender and insulin levels at baseline as predictors for changes in IGF-I levels, and gender, height and lean body mass (LBM) at baseline as predictors for changes in BC. The accuracy of the equations obtained by LR to predict whether a patient will be a GR or PR was 70% for IGF-I and 80% for BC responses. The d3 allele polymorphism in the GHR gene did not influence IGF-I levels and BF at baseline and their changes after GHRT. At baseline, distinct SNPs of the cholesteryl ester transfer protein (CETP) gene were associated with higher total cholesterol (TC), HDL-C and LDL-C, those of the apolipoprotein E (APOE) gene with lower TC and LDL-C, APOB gene with higher serum HDL-C, and those of the peroxisome proliferator-activated receptor gamma (PPARG) gene with lower LDL-C and the APOE/C1/C4/C2 cluster with lower tryglicerides (TG). After GHRT, greater reductions in TC and LDL-C were associated with SNPs in the APOB and PPARG, explaining 5% of the variation. SNPs in the signal transducer and activator of transcription 5B (STAT5B), in the phosphoinositide-3-kinase, catalytic, beta polypeptide (PIK3CB) and in the sodium/potassium/chloride transporter member 1 (SLC12A1) genes were associated with differences in ECW in GHD patients. We conclude that gender, body height, LBM and insulin levels were the best predictors of IGF-I and BC responses to GHRT in GHD adults. The presence of the d3-GHR allele did not influence responses to GHRT, but we found that some SNPs in genes related to lipid metabolism, GH signaling pathways and water balance impact the baseline characteristics of GHD and their response to GHRT.

KEYWORDS: growth hormone deficiency, hypopituitarism, growth hormone replacement therapy, prediction models, candidate gene approach, polymorphisms, body composition, growth hormone receptor, lipid metabolism, extracellular water, pharmacogenomics

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