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”Methodological and Clinical Studies on Insulin Resistance in Childhood”

Plats: M63, Karolinska Universitetssjukhuset i Huddinge
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Huvudhandledare: Dr Svante Norgren
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Insulin resistance is a condition in which adequate amounts of insulin fail to give an adequate response in target tissues. This thesis is based on five different studies, aiming to investigate different aspects of insulin resistance and the assessment methods thereof in children and in adults. The rationale for performing these studies is that insulin resistance is a key component of the metabolic syndrome and crucial in the development of type 2 diabetes. Concomitant with the increase in obesity worldwide, insulin resistance has become an important and increasingly more common pathological condition, which needs to be efficiently diagnosed and treated.

• In Study I we investigated proxy measures of insulin sensitivity assessment as compared to the reference standard Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT) in obese children and adolescents. The Homeostasis model assessment (HOMA-IR), the Quantitative Insulin Sensitivity Check Index (QUICKI) and fasting insulin were compared to the Sensitivity index (Si) of the FSIVGTT with the sample stratified by sex, puberty status and median of Si. This study demonstrated that fasting indices have a low validity in identifying insulin resistance in this group, and we generally discourage the use of these methods.

• Study II was performed in the same obese pediatric population with the aim of showing that HOMA-IR and QUICKI are interchangeable. The numerous comparisons between these methods should thus be avoided. Also, the high physiologic fluctuations in insulin levels further undermine the robustness of these methods. Studies I-II provide evidence that fasting indices as simple screening tools for insulin resistance in children and adolescents should, if used at all, be interpreted with caution.

• The third and fourth studies were performed with the aim of developing and validating models for the kinetics of C-peptide and Nonesterified fatty acids (NEFAs) respectively during an intravenous glucose challenge. An insulin modified FSIVGTT was performed on healthy normal weight young adults, with sampling of C-peptide and NEFAs included at all sampling points. In Study III a model was developed which assesses first phase C-peptide secretion, indirectly also estimating insulin secretion. Assessing insulin secretion is useful in

understanding diabetes development, in assessing progression to a diabetic state and in monitoring the effect of therapeutic regimens.

• In Study IV a novel NEFA model was validated on a subject level, with curves well fitting the diverse range of NEFA responses to a glucose challenge. Validation of the model using static parameters derived from the dynamic counterparts showed high correlation of the model's dynamic parameters to static parameters. NEFA levels are elevated in insulin resistance and affect glucose homeostasis on both the short and long term. This NEFA model may provide a complementary way of estimating insulin sensitivity, with focus on the lipotoxic aspect of diabetes development.

• Study V provides a clinical perspective on insulin sensitivity by examining metabolic features of a cohort of long-term cancer survivors treated with stem cell transplantation including total body irradiation, as compared to healthy controls matched for age and sex. The study shows an intact β-cell function, but decreased insulin sensitivity, after a median follow-up of 18 years. An adverse body composition with higher proportion fat mass than in controls was seen in cancer survivors.
Lower levels of growth hormone, higher levels of leptin and lower levels of adiponectin were found, all of which may explain the adverse body composition and the reduced insulin sensitivity.

In summary, several aspects of insulin resistance and insulin secretion have been studied existing methods of insulin secretion and sensitivity assessment have been investigated and implemented, and new methods described. We hope this will contribute further knowledge on diabetes development and
treatment strategies.

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