**Dr. Eniko Felszeghy** METABOLIC ALTERATIONS IN CHILDHOOD OBESITY/Role of insulinresistance/hyperinsulinaemia and clinical impact of acanthosis nigricans. University of Debrecen Doctoral School of Health Sience

**Background**. Obesity is the most common nutritional disease, and it is a major public health problem in many countries. It causes ill health and early death, and its metabolic consequences lead to increased liability to development of T2DM and cardiovascular disease. The prevalence of childhood and adolescent obesity has been increasing in the last decade over the world. Its associations with alterations of glucose and lipoprotein metabolism have been documented, and insulin resistance and hyperinsulinism were implicated in these associations. Acanthosis nigricans can be found in childhood obesity, it can be associated with insulin resistance, and it has been arisen as a physical marker of insulin resistance. **Aims.** Our studies demonstrated in the dissertation were aimed to determine the prevalence of alterations of glucose and lipoprotein metabolism in Caucasian-European obese children, to investigate the role of insulin resistance and hyperinsulinemia in development of these alterations, and to evaluate the impact of AN on development of these metabolic consequences of childhood obesity. **Patients and methods.** Obese children referred to obesity clinic were included into the studies. Their BMIs were over the 97$^{th}$ BMI percentile and BMI SDS values were >2, according to sex and age. Oral glucose tolerance test (OGTT) was performed, insulin levels were measured, insulin resistance/sensitivity indexes were calculated, and lipoprotein parameters as well as atherogenic factors associated to HDL-C were also investigated. **Results.** In our studies the frequencies of IFG, IGT and T2DM were in accordance with other European studies performed in childhood obesity. Insulin resistance, based on elevated HOMA-IR, basal and reactive hyperinsulinemia were found in vast majority of the investigated children. The fact that alteration of glucoregulation was substantially less than insulin resistance, basal and reactive hyperinsulinemia, suggests that hyperinsulinemia can successfully compensate for insulin resistance in the majority of obese children. Since IFG was less frequent than IGT, there is a need for performing OGTT to demonstrate abnormality of glucoregulation in obese children. In obese adolescents insulin resistance and hyperinsulinemia essentially due to the obesity itself, however puberty can also contribute to their development. Obese children investigated in our studies were characterised a rather high frequency of atherogenic dyslipidemia, i.e. elevated TG and decreased HDL-C levels. Paraoxonase, LCAT and CETP activities as well as ICAM1 and VCAM1 concentrations did not differ in the groups with normal or decreased HDL-C level. However, the results suggest that atherogenic dyslipidemia has a complex influence to the parameters of HDL function in childhood obesity. Evaluating the role of insulin resistance and hyperinsulinemia, positive correlations were found between HOMA-IR and 120'INS, ΣINS, 120'BG as well as ΣBG. Similarly, positive significant correlations were found between HOMA-IR and T-C as well as TG, and a negative one between HOMA-IR and HDL-C. In addition, significant associations were demonstrated between reactive insulinemia and reactive blood glucose parameters, and it was also found that reactive insulinemia was associated with atherogenic dyslipidemia, using multiple linear regression analysis. These results prove a determining role of insulin resistance in developing abnormal glucoregulation and dyslipidemia. In our study 120' INS and ΣINS values were significantly higher in obesity with AN than in simple obesity. HOMA-IR did not differ in the two groups but ISI was lower in OAN compared to SO. The frequencies of abnormal basal and reactive hyperinsulinemia, IFG and IGT as well as increased HOMA-IR values did not significantly differ in the two subgroups, although ratios of abnormal results were higher in cases with AN. However, it was ascertained that all children with severe AN (grade 4) had an increased HOMA-IR. These results prove an important role of the reactive hyperinsulinemia in development of AN, and they suggest that in the cases with sever AN the probability of insulin resistance is high. As regards to lipoprotein metabolism, significant differences were found in TG and HDL values between the subgroups of SO and OAN. In addition, the frequencies of increased TG and decreased HDL-C were higher in the subgroup of OAN compared to SO. These results suggest that atherogenic dyslipidemia can be more pronounced in childhood obesity if it is associated with AN. **Conclusion.** Insulin resistance, basal and reactive hyperinsulinemia are frequent conditions in childhood obesity, frequency of IGT is also rather high. These metabolic factors can be considered as risk factors for development of T2DM. Dyslipidemia is also a frequent condition in childhood obesity. Insulin resistance and hyperinsulinemia play an essential role in its development. Dyslipidemia in childhood obesity is a risk factor of artherosclerotic cardiovascular

disease, since atherosclerosis starts at childhood. Severe AN in childhood obesity can be considered as a physical marker of insulin resistance, and obese children with AN have to be investigated for alteration of glucoregulation and dyslipidemia.
**Keywords: childhood obesity, insulin resistance, acanthosis nigricans**