CHILDHOOD OBESITY: CAUSES AND CONSEQUENCES

PhD Thesis

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INTRODUCTION

An alarming rise in overweight and obesity was observed worldwide, particularly during the 1990's, in both the developed and developing countries. Obesity is a serious health risk; it is a major determinant of different diseases such as diabetes mellitus, hypertension, heart and kidney failure, atherosclerosis, cancer, infertility, birth complications and arthritis.

On the other hand, obesity is largely preventable through changes in lifestyle. The prevalence of childhood obesity continues to increase at a rapid rate. In the United States the National Health and Nutrition Examination Survey IV (1) showed that 13-14 % of children aged 6-11 years (yr) and adolescents aged 12-19 yr were overweight, while data from 1999-2000 indicated continued increases to 15.3 % of 6- to 11-yr-olds and 15.5 % of 12-to 19-yr-olds (2). In three cross-sectional studies of England and Scotland in 1974, 1984, 1994, only minor changes were found in the prevalence of overweight or obesity between 1974-84, but by 1994, the prevalence had risen by 9-10 % in boys, to over 13 % of English girls and to nearly 16 % in Scottish girls (3). Similar trends have been seen in other developed and developing countries. In Hungary, the prevalence of obesity increased from 12% to 16 % between 1980' and 1990's among schoolchildren (4).

Obesity is a heterogeneous group of conditions with multiple causes. Body weight is determined by an interaction between genetic, environmental and psychosocial factors. Although genetic differences are of great importance, the marked rise in the prevalence of obesity is best explained by behavioural and environmental changes.

Identical twins of obese parents are more likely to become obese than those of non-obese parents, suggesting a genetic factor to obesity. In a review on twin, adoption and family studies, body mass index (BMI) inheritance has been proposed to account for 25 % to 40% of the inter-individual variability (5).

Obesity is one of the features accompanying numerous genetic syndromes, like Prader-Willi (PWS), Cohen, Alstrom and Bardet-Biedl syndrome that have been genetically mapped (6). The first gene identification in obese human subjects was linked with the screening for genes identified previously in rodent models of monogenic obesity. These rodent models mostly involved genes in the regulatory pathway of food intake, which is mostly similar in human monogenic obesity (7). However, the genetic susceptibility to obesity is in most cases polygenic, and is

rarely the result of a Mendelian gene (monogenic obesity). Apart from rare obesity-associated syndromes, the genetic influences seem to operate through susceptibility genes. Such genes increase the risk of developing a characteristic but are not essential for its expression or, by themselves, sufficient to explain the development of a disease. The susceptible-gene hypothesis is supported by twin studies in which pairs of twins were exposed to periods of positive and negative energy balance, and the differences, for example, in the rate and the proportion of weight gain showed greater similarity within pairs than between pairs (8), which can suggest differences in genetic susceptibility within a population. One of the two approaches to identify susceptibility genes is the candidate gene approach. It involves testing the association between obesity and a specific allele of a gene either in a family study or in a large cohort of unrelated controls and patients. Several candidate genes have been associated with human obesity and its metabolic complications, which include e.g. receptors that are important in thermogenesis (β3-adrenergic receptor /3-BAR / gene and the family of uncoupling proteins), as well as those involved in appetite regulation.

The effects of catecholamines are modulated through four subtypes of adrenoreceptors (9). The human 3-BAR is expressed predominantly in visceral fats, where it plays a role in determing the resting metabolic rate through its ability to stimulate lipolysis and thermogenesis (10). The involvement of 3-BAR in energy metabolism originates from observations indicating the prevalence of the genetic variant at the codon 64 of the 3-BAR gene leads to replacement of a tryptophan with an arginine (Trp64Arg). This polymorphism has been reported to be associated with abdominal obesity (11), a propensity for weight gain (12), high BMI (13,14), insulin resistance (11,14) and an earlier onset of type 2 diabetes mellitus (11, 15). Other studies, however, could not demonstrate these associations (16,17).

An obese child will remain obese in adulthood and become at risk for acquiring or increasing coronary heart disease in 30 % to 60 % of cases (18). Although genetics may have a part of it, several environmental factors affect this phenomenon significantly. The first contact of the child with the environment is in the uterus. Over- or under-feeding in pregnancy has been associated with the development of obesity in later life (19,20). Beside of the prenatal period, the other critical period is the adolescence in the development and persistence of overweight in the paediatric age group. The period of ’adiposity rebound’ may constitute a third. It is when the

BMI begins to increase after reaching a nadir in early childhood. After birth the method of feeding may influence the risk of obesity. Family lifestyle and food habits play a role in children's food preferences and physical activity which may affect their body weight. Small for gestational age (SGA) has been associated with increased risk of diseases such as diabetes or cardiovascular disease in adulthood (21,22,23,24). Infants with high birth weights appear to have an increased risk of subsequent overweight (20).

The presence of inherited and acquired thrombophilias has recently been linked to most cases of maternal venous thrombotic events as well as these adverse obstetric outcomes (25). One of the most common inherited thrombophilias is heterozygosity for the factor V Leiden mutation. Although there is no consensus on the association between the factor V Leiden mutation and early pregnancy loss, but the evidence suggests an association between the mutation and late (first-, second-, third-trimester) fetal loss, severe preeclampsia, abruption and severe intrauterine growth retardation (IUGR) (26,27,28,29,30).

Over the past two decades, many papers have demonstrated that low birth-weight, thinness and short body length at birth are associated with increased risk of atherosclerosis, type 2 diabetes mellitus (T2DM), hypertension and metabolic syndrome. This observation, which originated at Hertfordshire in the United Kingdom (21,22,31) was confirmed in other countries such as Sweden (32) and Netherlands (33). The association of low birth-weight with adult cardiovascular disease led to the 'fetal origins or thrifty phenotype hypothesis' formulated by Barker (34). According to this hypothesis, an impaired intrauterine milieu, such as nutrient restriction , causes a 'reprogramming' of the endocrine-metabolic status of the fetus, which has short-term survival benefits, but this reprogramming can be detrimental effects on long term. If the prenatal nutrient restriction is subsequently followed by an extrauterine nutrient abundance, the risk of the development of metabolic syndrome increases, because this reprogramming consist mainly of the development of insulin resistance (23,35,36,37). There are, however contradictory results (38,39,40). Many researchers dispute the 'fetal origins hypothesis', asserting that environmental (e.g. maternal smoking, drug abuse, abnormal BMI etc) and genetic factors can, at least in part, explain the association between SGA and adult cardiovascular risk (41,42). Several pathophysiological mechanism are implicated, but in addition to the intrauterine retardation the sudden break of fetal development

and the accelerated pace of postnatal 'catch-up' growth might also play a role in the pathogenesis of these chronic diseases (23,42,43,44,45,46).

Obese children have a higher prevalence of T2DM and insulin resistance (47,48,50) and the frequency of this complication appears to have risen in recent years paralleling the worldwide increase in obesity in this age group. On the basis of the available data, the prevalence of T2DM in Caucasian children and adolescents (49,50,51,52) seems to be much lower then those reported in other races (53,54), but more representative, population-based surveys are needed. Although the presence of impaired glucose tolerance and chemical diabetes in obese children has been reported as early as the 60s, 70s of the last century (55,56,57), but it has become a hot topic only recently. Sinha et al. (58), in a multiethnic cohort of 167 obese children and adolescents demonstrated abnormal glucose tolerance in 25 % of children and 21 % of adolescents. According to the European literature, the first case of childhood T2DM in Europe was diagnosed in 1993 (59). Only two population-based reports have been published, by Rami et al. from Austria (60) and Ehtisham et al. from the UK (61). In April 2002, a questionnaire was distributed among European Childhood Obesity Group (ECOG) representatives from 16 European countries, which included several questions concerning the prevalence, risk factors and complications of childhood obesity, such as T2DM. From nine countries, altogether 184 European children were diagnosed with T2DM, 144 of them of Caucasian origin. The majority of them were overweight females and had positive family history for T2DM (62). Though both genetic and environmental factors play a role in the pathophysiology of T2DM, its rapidly increasing rates cannot be attributed to an altered genetic pool but rather to the raising prevalence of obesity.

Although general principles of treatment of T2DM in adolescents are similar to the treatment of adults there is general agreement between the paediatricians dealing with this problem that they should not be a simple extrapolation (50, 63, 64). Treatment strategies should be based on symptoms at presentation. Asymptomatic children identified at routine testing should be counselled on the necessary lifestyle changes. Therapeutic strategies include lifestyle and behaviour modification, nutrition education, and psychological and family therapy interventions. Because obesity is the major problem in most adolescents with T2DM, dietetic advice is mandatory, although calorie intake should not be too restricted to ensure normal growth and pubertal development. Patients should be encouraged to increase their

physical activity or at least to decrease inactivity. However, if the treatment goals are not achieved, pharmacological therapy should be considered. Recently, metformin has been approved by Food and Drug Administration (FDA) for use in children, and has been recommended by the American Diabetes Association (ADA) as a first line oral agent for treatment of T2DM in children (65,66). In symptomatic youth, particularly if ketonaemia develops, insulin treatment should be initiated to achieve good glycaemia control.

Childhood onset of adult cardiovascular disease has become a significant public health problem that needs to be addressed globally and individually. Whether genetic, environmental, or fetal influences are the primary culprits in the epidemic of obesity-related adult cardiovascular diseases seen today remains unknown. In spite of this, the interventional focus should be placed on early life, and health care providers and public health professionals should pay attention to the elevated future coronary heart disease risk among children. Better understanding of the aetiology of these diseases hopefuly will lead to more effective, targeted preventive measures and therapy.

AIMS

1. Trp64Arg polymorphism of the β3-adrenergic receptor gene

1.1 To examine the frequency of Arg64 allele of the β_3-adrenergic receptor (3-BAR) gene, which is one of the known candidate genes, in healthy and obese Hungarian children.

1.2 To look for possible associations between this polymorphism and some clinical and metabolic characteristics of obese children.

2. Leiden mutation; size at birth and later risk factors

2.1 To test the prevalence of Leiden mutation in the mothers of premature infants and in the mothers of intrauterine-growth-retarded children.

2.2 To determine the association between size at birth and later risk factors (hypertension, hyperinsulinism, hyperglycaemia, dyslipidaemia) in prepubertal children.

3. Impaired glucose tolerance and type 2 diabetes mellitus

3.1 To examine the prevalence of impaired glucose tolerance (IGT) and T2DM in obese Hungarian children.

3.2 To assess the effects of a 6-month diet and life-style changes in the children with IGT and T2DM.

SUBJECTS

Written informed consents were obtained from the subjects and all parents of the children before enrollment in the different studies. All of the studies were approved by the ethic review committee of the University of Pécs.

1.1 In all, 295 obese children (male:168) were included in the study after the exclusion of any endocrinological disorder, nutritional-, growth- and renal problems or obesity syndromes. With the exception of obesity, the children had no apparent disease and were not taking any kind of medication. A total of 147 healthy, non-obese children (male: 68) recruited from elementary schools, served as controls. The average age of the children in the two groups was 12.6±3.2 and 12.4±1.7, respectively.

1.2 Obese children carrying the Arg64 allele (n=35, male: 23) were compared to randomly chosen, obese children without the Arg64 allele (n=35, male: 20).

2.1 White (Caucasian) mothers of premature (Group PM; n=50) and mothers of intrauterine growth retarded neonates (Group IUGR; n=56) were tested. The newborns were considered as premature when their gestational age was < 37 weeks. Intrauterine growth retarded children were born full term with birth weight, height and head circumference below the 10^{th} centile (proportional) or with birth weight below the 10^{th} centile, but with normal length and head circumference (disproportional).

2.2 229 children (134 boys, 95 girls) were examined at the age of 6-10. We compared children born full term with normal weight, height and head circumference (1st group), the children born full term with birth weight, height and head circumference less than 10th centile (2nd group), children born full term with birth weight less than 10th centile and with normal length and head circumference (3rd group) and children who were preterm at birth (4th group) according to the criteria by Fekete et al (67). The age of children at the time of investigation was comparable in the four groups.

3.1-2 Oral glucose tolerance test (OGTT) was performed in 289 obese (153 boys) (mean BMI±SD: 31.1±4.6 kg/m^2) adolescents (mean age±SD, 12.9±2.7 years). After 6 months, the OGTT was repeated in children with IGT and DM.

METHODS

Anthropometric measurements

These investigations included weight, height and skin-fold thicknesses. Weight was obtained with subjects wearing light clothing to the nearest 0.1 kg on a standard beam scale. Height was measured to the nearest 0.1 cm by a Holtain stadiometer. In all examinations, children were considered as obese if their body weight exceeded the expected weight for height with more than 20%, and if body fat content with more than 25% in males and 30% in females. BMI was calculated according to the formula, real weight (kg)/height^2(m^2), while body fat (BF) was estimated from skinfold measurements, which were performed with a Holtain caliper, using Parizkova and Roth's formula (68). The body weight of control, healthy children was less than 120% of the expected weight for height.

Blood pressure measurements

Blood pressure (BP) was measured using a Mercury sphygmomanometer with proper cuff size in standard conditions. Blood pressure measurements were carried out according to the method recommended by the report in children (69,70). 3-5 occasional BP values were obtained and if the average of the blood pressure values was above the 95th centile for age and sex, 24 h ambulatory blood pressure monitoring (ABPM) was performed with a non-invasive recorder (Meditech, Hungary) using oscillometric method. Systolic, diastolic BP and heart rate values were also monitored with a sampling time set 20-minutes during daytime, and 30-minutes during sleep. The duration of these periods were adjusted to the individual timetable of the child. Those children whose mean 24h arterial blood pressure value exceeded the 95th centile value for height and sex (71) were considered hypertensive. (In the study of prepubertal children who were intrauterine growth retarded neonates, there was no possibility to perform the ABPM, so we considered children to be hypertensive when the lowest blood pressure value of the three measurements was above the 95th centile for age and sex (72).)

Laboratory tests

Determination of the Trp64Arg polymorphism in exon 1 of the 3-BAR gene

DNA was prepared from peripheral blood leukocytes by salting out procedure (73). Exon 1 was amplified with polymerase chain reaction (PCR) using the primers B*st*N UP: 5'-CGCCCAATACCGCCAACAG-3' and B*st*N DOWN: 5'-CCACCAGGAGTCCCATCACC-3' (product size 210 bp).

PCR reaction was performed in a 50 µl reaction volume with 50-100 ng genomic DNA, 10 pmol of each primer, PCR buffer containing 10 mmol/l Tris-HCL (pH 8.8), 50 mmol/l KCl, 1,5 mmol/l $MgCl_2$, 0,1% Triton X-100, 1 U Taq polymerase, 200 µmol/l dNTP.

PCR conditions were denaturising at 94 ºC for 3 min, followed by 33 cycles of denaturising at 94 ºC for 30 s, annealing at 64 ºC for 15 s, and extension at 72 ºC for 20 s with final extension at 72 ºC for 4 min.

Restriction enzyme analysis: 35 µl of PCR product was digested in a 50 µl volume containing 9,1 µl deionised distilled H_2O, 0,5 µl BSA (10 mg/ml), 0,4 µl enzyme MvaI (an isoschizomer of B*st*NI, MBI Fermentas, 10 U/µl) and 5 µl of reaction buffer R (MBI Fermentas) and incubated at 37 ºC for 4-18 h.

Restriction enzyme digestion products were separated on a 3% agarose gel and visualized by staining with ethidium bromide.

Digested fragments were 97, 61, 31, 15 and 6 bp for normal homozygote; 158, 97, 61, 31, 15 and 6 bp for Trp64Arg heterozygote; and 158, 31, 15, and 6 bp for Arg64Arg homozygote (74).

Determination of factor V Leiden mutation

The factor V Leiden mutation was tested from dried blood-spot samples according to Zöller and Dahlbäck (75), by PCR method. The sequences of the PCR primers (Ransom Hill Bioscience, Ramona, CA) for the amplification were the following: forward primer: 5'GGGCTAATAGGACTACTTCTAATC3'; reverse primer: 5'TCTCTTGAAGGAAATGCCCCATTA3'. PCR amplification was carried out in a final volume of 100 µl consisting of 10 µl DNA extract, 25 pmol from both primers, 200 µmol/l dNTP (Pharmacia), 20 mmol/l Tris-HCL pH 8, 50 mmol/l KCl, 2.5 mmol/l $MgCl_2$, 1.5 U Taq polymerase (Gibco or Promega). PCR conditions were 5 minutes at 94 °C, followed by 30 cycles of 94 °C for 40 seconds, 55 °C for 1 minute

and 72 °C for 1 minute. Final extension was at 72 °C for 5 minutes. The DNA was digested by MnI restricted enzyme (Stratagene). The resulting PCR products were separated by electrophoresis on a 2.2 % agarose gel with ethidium-bromide staining.

Biochemical studies

Plasma glucose, serum insulin and lipid levels were determined from blood samples taken after an overnight fast in obese children. In obese children OGTT (1.75 g/kg ideal body weight, max. 75 g) was performed. Plasma glucose and serum insulin levels were determined at 0 and 120 min at the OGTT by the glucose oxidase method and by commercially available radioimmunoassay (RIA) kits, respectively. C-peptide level was also determined by RIA. The criteria of impaired glucose tolerance and diabetes mellitus were based on the recommendation of American Diabetes Association (76). Insulin resistance was estimated by the Homeostasis Model Assessment (HOMA) using the formula: fasting serum insulin (μIU/ml) x fasting plasma glucose (mmol/l)/22.5 (77). (In the study of prepubertal children who were intrauterine growth retarded neonates, the cutoff value for fasting insulin was 20 μIU/ml, while hyperglycaemia was considered when the fasting blood glucose level was more then 6.2 mmol/l.)

Serum cholesterol and triglyceride levels were determined by the enzymatic method with Boehringer kits; serum high-density lipoprotein (HDL) cholesterol was measured according to the method of Steele et al. (78). Serum cholesterol, triglyceride and HDL-cholesterol were considered high or low when they fell above or below the recommended values of the Hungarian Lipid Consensus Conference (79): serum cholesterol > 5.2, HDL-cholesterol < 0.9 mmol/l and serum triglyceride > 1.1 mmol/l (< 10 years)- > 1.5 mmol/l (> 10 years). If the value of any of these parameters was abnormal, the child was considered dyslipidaemic.

Statistical analysis

All statistical analysis were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 7.5, 8.0 and 10.0. Data are presented as means±SD. Statistical significance of the differences between groups was evaluated using the Fisher's exact or Chi-square or Student's t-test or ANOVA, when appropriate.

RESULTS

1. Trp64Arg polymorphism of the 3-BAR gene

(8, 11, 13, 14; abstr: 2,6)*

1.1 The frequency of Trp64Arg polymorphism in normal and obese Hungarian children was similar. The mutation occurred in 14 healthy (male: 7) and 35 obese children (male: 23), of whom 2 were Arg64Arg homozygote and 33 were Trp64Arg heterozygote.

1.2 The obese children with Arg64 allele were compared to a group of obese children without it. The latter group was formed by a computer-generated randomisation. The anthropometric data of obese children with and without polymorphism are shown in Table 1.

Table 1. Anthropometric data of obese children with and without polymorphism (mean±SD)

	Trp64Trp (n=35) (male: 20)	**Trp64Arg/Arg64Arg (n=33+2) (male: 23)**
Age (years)	12.3 ± 2.9	12.6 ± 2.9
Body height (cm)	155.7 ± 15.9	161.4 ± 15.4
Body weight (kg)	75.6 ± 17.7	81.2 ± 23.2 **
BMI (kg/m^2)	30.9 ± 3.9	35.0 ± 10.9 ***
BF (%)	36.5 ± 2.3	38.8 ± 3.9 ***
Systolic blood pressure (mmHg)	114.5 ± 8.3	125.2 ± 10.1 *
Diastolic blood pressure (mmHg)	72.5 ± 9.0	73.2 ± 8.4

**** p < 0.05, ** p < 0.01, * p < 0.001 BMI: body mass index; BF: body fat*

The weight of obese children with Arg64 allele was significantly higher ($p<0.01$) than those without the polymorphism. Similar tendency ($p<0.05$) was observed in the BMI and BF values. Laboratory results are shown in Table 2.

*Numbers in parenthesis are serial numbers of the papers and abstracts which were written in the issue of the thesis.

Table 2. Metabolic parameters in obese children with and without polymorphism (mean±SD)

	Trp64Trp (n=35)	**Trp64Arg/Arg64Arg (n=33+2)**
Plasma glucose (mmol/l) 0 min	4.4±0.8	4.5±0.9
Plasma glucose (mmol/l) 120 min	6.6±1.8	6.3±1.3
Serum insulin (μIU/ml) 0 min	16.9±7.6	31.4±16.7*
Serum insulin (μIU/ml) 0 min [x]	21.6±2.5	31.2±16.4*
Serum insulin (μIU/ml) 120 min	120.0±71.7	101.6±90.2
HOMA	3.2±1.8	6.2± 3.9*
HOMA [x]	3.8±1.3	6.1± 3.8*
Serum cholesterol (mmol/l)	4.6±0.8	4.3±1.1
Serum triglyceride (mmol/l)	1.4±0.8	1.4±0.6
Serum HDL-cholesterol (mmol/l)	1.2±0.3	1.2±0.2

*X adjusted for body fat, * p < 0.001 HOMA: Homeostasis Model Assessment*

The serum insulin levels and HOMA were significantly higher in children carriers of Arg64 allele as compared to those not having this. Since the two groups were significantly different in respect of BF and BW, and these factors are closely related to insulin levels and HOMA index, therefore these latter two parameters were corrected for BW and BF. The corrected values remained significantly different between the two groups. Serum triglyceride, total cholesterol and HDL-cholesterol levels were not different between the two groups. Systolic BP of subjects with Trp64Arg and/or Arg64Arg genotype was also significantly higher ($p<0.001$) than that of those with the Trp64Trp genotype (Table 1.).

2. Leiden mutation; size at birth and later risk factors
(3,4,5)

2.1 The prevalence of the Leiden mutation in an apparently healthy Hungarian Caucasian population sample of our region was 6.33 % (80), which was comparable with other European prevalence rates (81). In the group with IUGR the prevalence of heterozygosity was not significantly different from that of the healthy Hungarian population, while in the preterm the prevalence was 18 %. As compared to the 6.3% prevalence rate of the healthy Hungarian population, this 18 % value of the mothers of premature neonates proved to be significantly higher ($p<0.01$). The difference between Groups PM and IUGR (18% versus 7.2%) was also significant statistically (Table 3).

Table 3. Prevalence of factor V Leiden mutation in the two groups

	Normal (% of total)	**Heterozygotes (% of total)**	**Homozygotes (% of total)**
Group PM (n=50) (mothers of prematures)	**41 (82)**	**9 (18)**	**-**
Group IUGR (n=56) (mothers of intrauterine growth retarded neonates)	**52 (92.8)**	**3 (5.4)**	**1 (1.8)**

Figures in parenthesis indicate percent of total.

2.2 According to the results cardiovascular risk factors cannot be found among children at the age of 6-10 who were born with low birth weight (Table 4 and 5). The anthropometric data of children are shown in Table 4.

Table 4. Anthropometric data of children at the time of examination (prepubertal stage) (mean±SD)

	Full term neonates			**Prematures**
	normal	**proportional IUGR**	**disproportional IUGR**	
	(n=24)	**(n=90)**	**(n=25)**	**(n=90)**
	1. group	**2. group**	**3. group**	**4. group**
Age (years)	**8.8±1.5**	**8.1±1.5**	**8.7±1.7**	**9.2±1.6**
BW (kg)	**32.2±7.4**	**24.9±7.2* ****	**28.0±8.6**	**30.1±9.2**
BH (cm)	**134.4±10.1**	**122.6±9.3 ****	**128.2±9.9**	**130.3±8.3**
BF (%)	**22.9±6.8**	**20.5±5.9**	**20.2±4.4 ****	**20.9±6.4**
LBM (kg)	**24.4±4.2**	**19.6±4.6* ****	**22.2±6.7 ****	**23.4±6.2**

**p<0.01, ** p<0.001*

BW: body weight, BH: body height, BF: body fat; LBM: lean body mass

BW: p<0.001 1. vs. 2. group; , p<0.01 2. vs. 4 group
BH: p< 0.001 1. vs. 2. 2. vs. 4 group
BF: p<0.001 1. vs. 3. group;
LBM: p< 0.001 1. vs. 2., 3. group, p<0.01 2. vs 4 group

Weight and height of the children in the 2nd group were significantly lower than in the 1st and 4th groups (2nd group vs. 4th group : $p< 0.01$; 2nd group vs. 1st group: $p<0.001$). The laboratory results were normal (Table 5). Dyslipidaemia was found 21% in the 1st group, 17 % in the 2nd group, 16% in the 3rd group and 28% in premature. There was no significant difference among the four groups. The mean of the systolic and diastolic blood pressures were similar in the four groups. Hypertension was detected in 12.5 % of the 1st and 3rd groups, in 5.6 % of the 2nd group and in 8.9 % of the 4th group.

Table 5. Laboratory results of children at the time of examination (mean±SD)

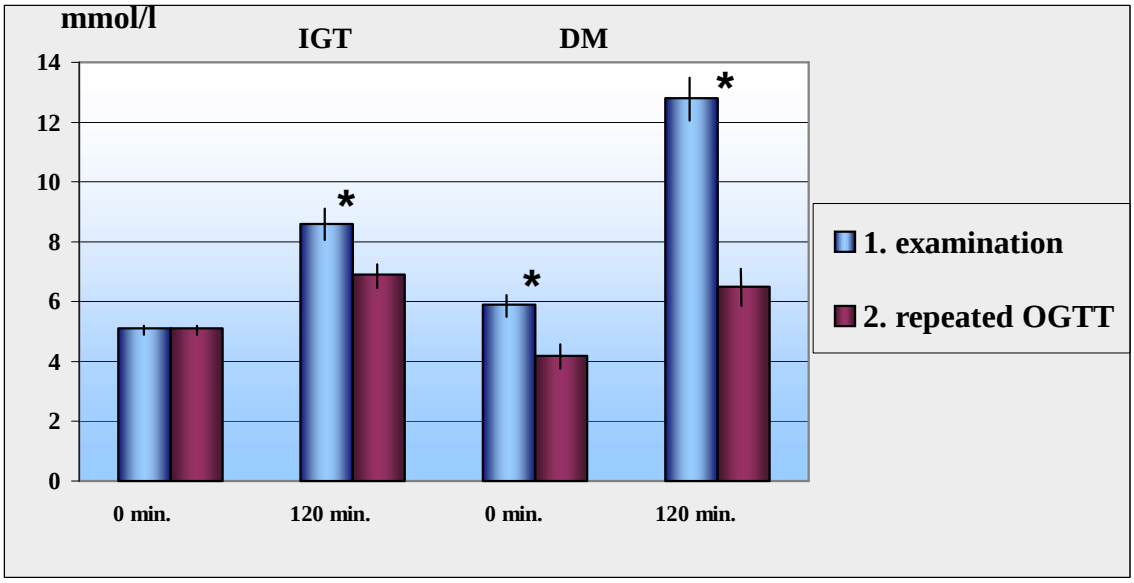
	Full term neonates			**Prematures**
	normal (n=24)	**proportional IUGR (n=90)**	**disproportional IUGR (n=25)**	**(n=90)**
	1. group	**2. group**	**3. group**	**4. group**
Blood glucose (mmol/l)	**4.9±0.8**	**4.6±0.6**	**4.8±0.8**	**4.6±0.5**
Insulin (μIU/ml)	**7.0±5.2**	**6.4±5.1**	**5.9±3.7**	**6.2±3.7**
Cholesterol (mmol/l)	**4.5±0.8**	**4.3±0.7**	**4.5±0.6**	**4.4±0.7**
HDL-chol. (mmol/l)	**1.5±0.3**	**1.6±0.3**	**1.7±0.4**	**1.6±0.3**
Triglyceride (mmol/l)	**1.0±0.4**	**0.9±0.3**	**1.0±0.4**	**0.9±0.4**
Systolic BP (mmHg)	**112.8±9.7**	**109.1±9.3**	**108.1±14.0**	**111.2±10.3**
Diastolic BP (mmHg)	**66.3±9.7**	**63.0±8.2**	**62.3±10.3**	**65.1±9.3**

3. Impaired glucose tolerance and type 2 diabetes mellitus

(1,2,6,7,9,10,12; abstr: 1,3,4,5,7)

3.1 Because of the scarce European, especially Hungarian data of the prevalence of T2DM our aim was to evaluate the frequency of IGT and T2DM among clinically healthy, obese children. IGT was found in 50 children (17.3 %), while the prevalence of T2DM was 1.7 % (n=5), so altogether the disorders of carbohydrate metabolism could be detected in 19.0 % of the children (n=55).

The children with disturbed carbohydrate metabolism, a low calorie (1500 kcal/day), carbohydrate (200-250 g/day) diet, and regular exercise were recommended and they were called back for a repeated OGTT after six months.

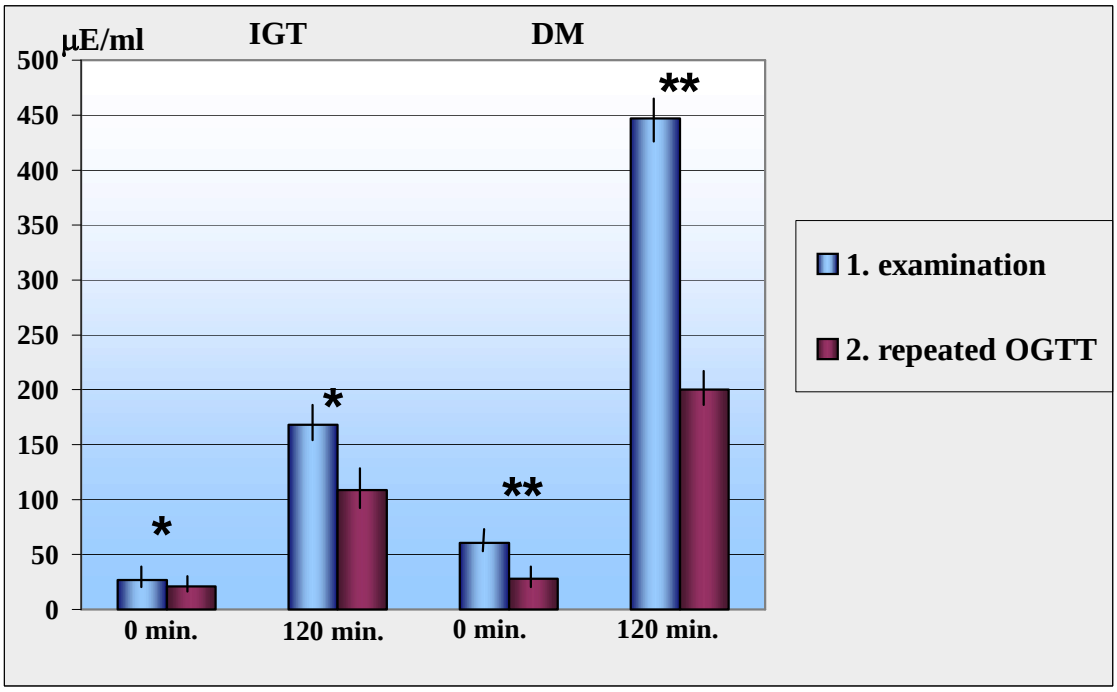


** p < 0.001*

Figure 1. Changes of blood glucose (mean±SD) after a 6-months diet and exercise (n=36)

3.2

32 children with IGT and 4 children with T2DM took part in the repeated OGTT. Although the body weight was not changed significantly, BMI decreased significantly (30.4±4.9 vs 29.0±4.4 kg/m2; p<0.05). The changes of mean blood glucose and serum insulin levels are shown in Figure 1 and 2.. HOMA index also decreased significantly (6.7±3.7 vs 4.9±3.3).



** p< 0.001 ** p< 0.05*

Figure 2. Changes of serum insulin levels (mean±SD) after 6-months diet and exercise (n=36)

DISCUSSION AND PRACTICAL CONSEQUENCES OF THE STUDIES

1. Trp64Arg polymorphism of the 3-BAR gene

According to the literature the frequency of Trp64Arg mutation of 3-BAR is highly heterogeneous among different populations. The frequency of the mutation was highest in the Pima Indians, followed by Japanese people and Caucasians in the USA (15) and France (12). There was no significant difference between the frequency of carrying the Arg64 allele of 3-BAR gene in healthy and obese Hungarian children. The frequency was 9.5 vs. 11.8 % in the two groups, respectively, which is similar to the frequency of this polymorphism in Europe (12,16,17). Our results are in concert with the findings of studies conducted in children, showing a significant difference between normal weight and obese children (16,82). Several studies have investigated the association of Trp64Arg polymorphism of the 3-BAR gene with obesity or weight gain, but the results are equivocal (83,84). The one possible reason for the contradiction can be the differences in the age and extent of obesity of the subjects in different studies. Only few studies (16,17,82) have looked at the effects of this polymorphism on obesity and cardiovascular risk factors in children. In our present study, the obese children with Trp64Arg and/or Arg64Arg genotypes had significantly higher fasting serum insulin levels, HOMA indices and systolic BP values than the Trp64Trp group. These differences remained significant when corrected for BW and BF. The significantly higher fasting serum insulin and HOMA values indicate the presence of insulin resistance, which together with high blood pressure are the main features of metabolic cardiovascular syndrome. However, the lipid levels were similar in the two obese groups. Our results are in concert with the findings of Sakane (85) and Strazullo et al. (86).

Observations and practical consequences

The frequency of Trp64Arg polymorphism was similar in Hungary as compared to other European countries, and there was no difference between healthy and obese children, however the possession of Arg64 allele in obese children is associated with higher degree of obesity, insulin resistance and hypertension, but the number of cases need to be increased and further studies are needed to clarify these associations.

To the best of my knowledge this is the first study of children in Hungary investigating the frequency of a candidate gene of obesity and its effect on cardiovascular risk factors.

Although, in the literature, there are controversial results of the role, not only, of Trp64Arg polymorphism of 3-BAR gene, but other candidate genes, in developing obesity, according to our findings and to know that obesity a multifactorial and heterogeneous disorder, therefore, preventive measures for obesity, to be fully effective in a population, must based on the modification of several potential risk factors simultaneously. Comprehensive, successful prevention programs are needed which should focus on promoting and supporting healthful lifestyles for all children at home, in school and in the society. The population strategies should harmonize lifestyle and nutritional habits with recommendations, by following the quality of family and social nutrition for changing it, education on healthy nutrition and physical activity. The individual level program management involves continuous longitudinal growth and nutritional status monitoring, identification of children with nutritive risk factors or with positive family history for obesity and for selective screening of metabolic parameters, and healthy lifestyle and nutrition counseling.

Although the genetic analyses of the samples started at the Department of Clinical Genetics and Child Development of University of Pécs, these investigations made the possibility to create a scientific PCR laboratory at the Department of Paediatrics of University of Pécs.

2. Leiden mutation; size at birth and later risk factors

As it was mentioned in the introduction, there has been considerable interest in the possibility that prenatal events could influence the adult life. Adults who were small at birth have been reported to have higher blood pressure and increased risk of death from ischaemic heart disease, although there are some contradictory results.

The prevalence of Leiden mutation was 7.2% in the mothers of growth retarded neonates and 18 % in the group of mothers of premature infants, the latter being significantly higher than the 6.3 % prevalence of this mutation in healthy Hungarian subjects ($p<0.01$). Our findings confirmed the results of Lindqvist et al (87), that the incidence rate of activated protein C (APC) resistance of women who had IUGR children did not differ from that in the healthy population.

Observations and practical consequences

Our results, however, are in concert with the findings of some studies that the presence of Factor V, Leiden mutation may have a role in premature delivery.

According to our results, cardiovascular risk factors cannot be proved among children at the age of 6-10 who were born as intrauterine growth retarded. Further studies are required to determine whether which stage of pregnancy might influence birthweight and later risk factors, and it can be important at what age of children should be examined for these risk factors.

3. Impaired glucose tolerance and type 2 diabetes mellitus

T2DM in children and adolescents is regarded as an emerging problem; however, there are few reliable reports of its true population prevalence or its prevalence in obese children. As the childhood population becomes increasingly overweight, T2DM may be expected to occur in younger, prepubertal children. The young age at presentation exposes these patients to a high risk of complications in adult life.

Observations and practical consequences

According to our prevalence data of T2DM, it seems that not it is the major problem among obese youth, in spite of this, clinically healthy obese children have disturbances of carbohydrate metabolism, so screening for T2DM in children and adolescents, as suggested by the American Diabetes Association, is highly recommended.

Impaired glucose tolerance and T2DM in asymptomatic obese children can be managed with dietary and lifestyle interventions, resulting improvement of the metabolic status of these children.

According to this observation and assuming that T2DM is preventable, there are two components of the primary prevention. First of all, a populations strategy is needed, for altering the lifestyle and the environmental determinants of T2DM. Second, a high-risk strategy is needed for screening individuals at especially high risk for T2DM and bringing preventive care to them.

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LECTURES AND POSTERS IN THE ISSUE OF THE THESIS

1. A Magyar Elhízásellenes Alapítvány VII. Konferenciája
   1996. szeptember 18-22., Balatonlelle
   Erhardt É, Molnár D: *Intrauterin tápláltság szerepe a felnőttkori elhízásban és a kardiovaszkuláris betegségekben*

2. 7th International Workshop of European Childhood Obesity Group
   21-22nd November, 1997, Verona, Italy
   E. Erhardt, D. Molnár: *Size at birth and later risk factors*

3. A Magyar Elhízásellenes Alapítvány XII. Konferenciája
   1999. szeptember 19-20., Siófok
   Erhardt É, Molnár D., Stankovics J., Márkus A., Török K.: *Intrauterin növekedés, kardiovaszkuláris rizikófaktorok, Leiden mutáció*

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   8-10th October 1999, Malmö-Lund, Sweden
   E. Erhardt, D. Molnár, J. Stankovics, A. Márkus, K. Török: *Intrauterine growth retardation, cardiovascular risk factors, Leiden mutation*

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   Erhardt É., Molnár D., Stankovics J., Török K.: *Kardiovaszkuláris kockázati tényezők, intrauterin növekedés, Leiden mutáció*

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   2001. május 18-19, Hortobágy, Máta
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7. Magyar Gyermekdiabetológiai szekció Tudományos Ülése
   2001. 09.27.-30., Zalakaros
   Erhardt É., Molnár D., Soltész Gy.: *Csökkent glucose tolerancia előfordulása kövér gyermekekben*

8. 8th Middle European Workshop on Paediatric Endocrinology (MEWPE)
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   E. Erhardt, M. Czakó, D. Molnár, Gy. Kosztolányi: *The Trp64Arg polymorphism of the beta3 adrenergic receptor gene in normal and obese Hungarian children*

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   E. Erhardt, M. Czakó, D. Molnár, Gy. Kosztolányi, G. Soltész: *The Trp64Arg polymorphism of the beta3-adrenergic receptor gene in normal and obese Hungarian children*

10. Magyar Diabetes Társaság XVI. Kongresszusa
    2002.05.30.-06.02., Debrecen
    Erhardt É., Csernus K., Molnár D., Soltész Gy.: *A 2-es típusú diabetes ritka, az IGT viszont gyakori tünetmentes, kövér gyermekekben*

11. 28th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD)
    18-21 September 2002, Graz, Austria
    E. Erhardt, D. Molnár, Gy. Soltész: *Impaired glucose tolerance and type 2 diabetes in obese Hungarian children.*

12. 12th European Congress on Obesity
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    E. Erhardt, M. Czakó, D. Molnár: *The Trp64Arg polymorphism of the beta3-adrenergic receptor gene in healthy and obese Hungarian children*

13. A Magyar Gyermekorvosok Társaságának 2003. évi Nagygyűlése
    2003. június, Szeged
    Erhardt É. Csernus K., Molnár D., Soltész Gy.: Szénhidrát-anyagcserezavarok kövér gyermekekben

14. 13th European Childhood Obesity Group Workshop
    25-27 September, 2003, Tenuta Moreno, Mesagne (BR), Italy
    E. Erhardt, D.Molnár: *A rare complication that can be ignored (felkért, plenáris előadás)*

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    2003. 10.17.-18., Szeged
    Erhardt E., Czakó M., Molnár D., Kosztolányi Gy., Soltész Gy.: *β_3-adrenoreceptor gén Trp64Arg polimorfizmus*

16. A Magyar Diabetes Társaság XVII. Kongresszusa
    2004. április 22-25., Tihany
    Erhardt É., Czakó M., Molnár D., Kosztolányi Gy., Soltész Gy.: *A beta-3-adrenoreceptor gén, Trp64Arg polimorfizmus előfordulása normál és kövér, magyar gyermekekben*.

17. 13th European Congress on Obesity
    26-29 May, 2004, Prague, Czeh Republic
    E. Erhardt E, K. Csernus, M. Czakó, D. Molnár: *Frequencies of single-nucleotude polymorphisms of some candidate genes playing role in thermogenesis in Hungarian children (poster).*

18. XIV. Symposium of Polish Pediatric Endocrinology
    15-17 October, 2004, Wisla, Poland
    E. Erhardt: Is type 2 diabetes mellitus a significant problem in European children? (felkért, plenáris előadás)

19. 14th European Congress on Obesity
    1-4 June, 2005, Athen, Greece
    E. Erhardt, K. Csernus, D. Molnár: *Examination of synergetic effects of some candidate genes playing role in thermogenesis (poster).*

20. ECOG International Workshop
    29 Sept-1 Oct, 2005, Vienna, Austria
    E. Erhardt, K. Csernus, Sz. Bokor, D. Molnár: Frequency and effect of Ala 12 allele of PPARγ on cardiovascular risk factors in Hungarian children (poster)

21. Obezitológiai szimpózium és továbbképző tanfolyam
    2005. október, Pécs
    Erhardt É: *A gyermekkori elhízás helyzete és kezelése (felkért előadás)*

22. Gyermekkori Diabetes és Obesitas Továbbképző Tanfolyam
    2006. március, Pécs
    Erhardt É: 2-es típusú diabetes mellitus (felkért előadás)

23. X. Családorvosi konferencia
    2007.10. 06., Budapest
    Erhardt Éva: Az elhízás genetikája (felkért előadás)

OTHER LECTURES AND POSTERS

1. A Magyar Elhízásellenes Alapítvány III. Konferenciája
   1994 szeptember, Balatonlelle
   Erhardt É., Molnár D.: *A bioelektromos impedancia analízis értékelése gyermekekben*

2. Magyar Gyermekorvosok Társaságának 1994. évi Nagygyűlése, Pécs
   1994 augusztus 29.-30.
   Erhardt É., Kardos M., Harangi F.: *Acne kapcsán fellépő musculoskeletalis szindróma két esete*

3. A Magyar Reumatológusok Egyesületének 1994. évi Vándorgyűlése Gyermekreumatológiai Szekció, Győr
   1994 október 6.-8.
   Erhardt É., Kardos M., Harangi F.: *Acne kapcsán fellépő musculoskeletalis szindróma két esete*

4. 4th International Workshop of European Childhood Obesity Group
   Nov. 1994, Pécs
   Erhardt É., Molnár D.: *Body composition of children by skinfold and BIA methods (poster)*

5. Nemzetközi Radiológiai Kongresszus, a Magyar Gyermekradiológiai Társaság szervezésében
   1995 szeptember, Szentendre
   Weisenbach J., Kozári A., Erhardt É.: *Hypophysis microadenoma diagnosztikus csapdái*

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   1995 szeptember, Balatonlelle
   Erhardt É., Molnár D.: *Hasznos támpontot nyújt-e a diétás felmérés az elhízás kezelésében ?*

7. A Magyar Atherosclerosis Társaság Gyermekszekciójának Ülése
   1995 október, Veszprém
   Erhardt É., Molnár D.: *Hasznos támpontot nyújt-e a diétás felmérés az elhízás kezelésében ?*

8. 6th European Congress on Obesity
   May 1995, Copenhagen, Denmark
   Erhardt É., Molnár D., Schutz Y.: No *blunted postprandial thermogenesis in obese adolescents (poster)*

9. 6th Annual Meeting of Alpe-Adria Study Group of Pediatric Endocrinology and Diabetology
   15th-16th December, 1995, Verona, Italy
   Erhardt É., Molnár D.: *No blunted postprandial thermogenesis in obese children*

10. 6th European Congress on Obesity
    May 1995, Copenhagen, Denmark
    Molnár D., Erhardt É., Csábi Gy., Schutz Y.: *Increased postabsorptive fat oxidation in obese adolescents*

11. A Gyermekendokrinológiai Munkacsoport ENDOPED-MILLECENTUM tudományos ülése
    1996.május 3-4., Szombathely
    Erhardt É., Kozári A., Decsi T., Juricskainé Dávid Zs., Soltész Gy.: Sporadikus és familiáris Addison-kór
    Kozári A., Erhardt É., Pintér A., Szilágyi K., Magyarlaki T., Kálmán E., Soltész Gy.:*Hashimoto betegség talaján kialakuló follicularis pajzsmirigy carcinoma*

12. Vth Congress of European Society for Pediatric Dermatology
    September 4-8, 1996, Rotterdam
    Erhardt É, Harangi F, Kardos M, Várszegi D: *Two cases of musculoskeletal syndrome associated with acne. (poster)*

13. 7th Annual Meeting of Alpe-Adria Study Group of Pediatric Endocrinology and Diabetology
    November 7-9th, 1996, Bolzano
    E. Erhardt, R. Hermann, A. Kozári, G. Soltész: *Familial, X-linked Addison disease*

14. A Gyermekendokrinológiai Munkacsoport ENDOPED tudományos ülése
    1997. április 24-26., Nyíregyháza
    Erhardt É., Horváth Örs P, Környei V., László T., Soltész Gy.: *Tartós hypertonia hátterében felfedezett gravis hypertensio*

15. A Magyar Elhízás Ellenes Alapítvány X. Konferenciája
    1997. szeptember 18-21, Dobogókő
    Erhardt É., Molnár D.: *A Prader-Willi syndroma új diagnosztikai lehetőségei molekulárgenetikai módszerekkel*

16. I. Slovak-Hungarian Symposium of Pediatric Endocrinology and Diabetology
    January 23rd-24th, 1998, Vyhne, Slovakia
    E. Erhardt, P. Horváth Örs, V. Környei, T. László, Gy. Soltész: *Case report of a phaeochromocytoma discovered in the background of a permanent high blood pressure*

17. A Gyermekendokrinológiai Munkacsoport ENDOPED tudományos ülése
    1998. május 14-16, Dobogókő
    Erhardt É., Sólyom J., Homoki J., Dávid Zs., Soltész Gy.: *Vérfolt 17-hydroxiprogeszteron és vizelet steroid profil vizsgálatok összehasonlítása adrenogenitális syndromában szenvedő gyermekekben*

18. Magyar Gyermekgyógyász Társaság Dél-dunántúli Területi Szervezetének Kongresszusa
    1998. szeptember 25-26., Mosdós
    Erhardt É., Sólyom J., Dávid Zs., Homoki J., Hermann R., Kozári A., Soltész Gy.: *Vérfolt*
    17-hyroxiprogeszteron és vizelet steroid profil vizsgálatok összehasonlítása adrenogenitális syndromában szenvedő gyermekek nyomonkövetésében

19. Pécs-Tübingen-Nürnberg Trilateral Symposium on Endocrinology
    May 2nd, 1998, Nürnberg, Germany
    Erhardt É., David Zs., Soltész Gy.: *Follow-up of adrenogenital syndrome in children based on plasma 17-OH-progesterone and urinary steroid metabolites*

20. Satellite Symposium of the 8th International Congress of Obesity
    4th September, 1998, Paris, France
    D. Molnár, T. Decsi, I. Burus, K. Török, É. Erhardt: *Effect of weight reduction on plasma total antioxidative capacity in obese children*

21. 8th International Child Neurology Congress, Pre-Congress Satellite on Rett syndrome
    11-12th September, 1998, Bled, Slovenia
    E. Erhardt, K. Hollódy, D. Molnár, K. Borvendég: *Body composition of Hungarian Rett syndrome girls (poster)*

22. Middle European Congress on Paediatric Endocrinology
    13-15th November 1998, Szépalma (Zirc), Hungary
    E. Erhardt, R. Hermann. S. Davidovics, E. Kálmán, A. Kozári, G. Soltész: *Graves disease associated with papillary thyroid carcinoma*
    R. Hermann, E. Erhardt, G. Soltész: Neurofibromatosis with Noonan's phenotype

23. Magyar Humángenetikusok Konferenciája
    1998. október 18-21., Szeged
    Erhardt É., Morava É., Decsi T., Czakó M., Kosztolányi Gy.: *Súlyos újszülöttkori hypotonia Prader-Willi regio deléciójával*

24. A Gyermekendokrinológiai Munkacsoport ENDOPED Tudományos Ülése
    1999. május 7-9, Szeged
    Erhardt É., Soltész Gy.: *Szükséges-e minden Turner syndromás gyermeket növekedési hormonnal kezelni ?*

25. A Magyar Humángenetikai Társaság II. Kongresszusa
    1999. augusztus 25-29., Pécs
    Erhardt É., Adamovich K., Vincellér M.: *Opitz C syndroma oesophagus atresiával*

26. Magyar Diabetes Társaság Gyermekdiabetológia szekció Tudományos Ülése
    1999. október 15-16., Győr
    Erhardt É., Kozári A., Hermann R., Harangi F., Soltész Gy.: *Dermatomyositis és diabetes együttes előfordulása*

27. Middle European Workshop on Paediatric Endocrinology
    19-21 November, 1999, Emmersdorf, Austria
    E. Erhardt, E. Morava, M. Czakó, T. Decsi: *Severe muscular hypotonia in a newborn infant*

28. A Gyermekendokrinológiai Munkacsoport ENDOPED Tudományos Ülése
    2000. május 12-13, Seregélyes
    Erhardt É., Hermann R., Kozári A., Kajtár P., Oberritter Zs., Tornóczky T., Soltész Gy.: *Virilizáló mellékvese tumor*

29. 11th European Congress on Obesity
    30 May-2 June 2000, Vienna, Austria
    H. Minda, T. Decsi, K. Török, E. Erhardt, I. Burus, Sz. Molnár, D. Molnár: Relationship between serum fatty acids and insulin sensitivity in obese children

30. A MGYT Dél-dunántúli Területi Szervezet Tudományos Ülése
2000. szeptember 22-23, Szigetvár
Erhardt É., Morava É., Adamovich K., Decsi T.: *Újszülöttkori izomhypotonia egy ritka syndroma kapcsán*

31. MGYT és a Magyar Diabetes Társaság Gyermekdiabetes Szekció Kongresszusa
2000. október 13-14., Miskolc-Lillafüred
Hermann R., Kozári A., Erhardt É., Soltész Gy.: *Diabetes, Addison kór és hypothyreosis együttes előfordulása*

32. A Magyar Reumatológusok Egyesülete Gyermekreumatológiai Szekció Ülése
2000.10. 27., Budapest
Erhardt É., Hermann R., Kozári A., Harangi F.: *Dermatomyositis előfordulása diabetes mellitusos betegben*

33. A Gyermekendokrinológiai Szekció ENDOPED Tudományos Ülése
2002. május 3-4., Győr
Erhardt É., Sólyom J., Kozári A., Hosszú É., Soltész Gy.: *Hyperinsulinaemiás hypoglycaemia és normoglykaemia*

34. Magyar Diabetes Társaság XVI. Kongresszusa
2002.05.30.-06.02., Debrecen
Erhardt É., Csernus K., Molnár D., Soltész Gy.: *A 2-es típusú diabetes ritka, az IGT viszont gyakori tünetmentes, kövér gyermekekben*

35. A Gyermekendokrinológiai Szekció ENDOPED Tudományos Ülése
2003. május 16-18., Salgóbánya
Erhardt E., Kozári A., Sárkány I., Kovács J., Soltész Gy.: *Újszülöttkori hyperthyrotropinaemia két esete*

36. Middle European Society for Paediatric Endocrinology (MESPE)
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