Obesity and related metabolic disorders: influence of genetic variability and nutritional factors

PhD Thesis

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Abbreviations

BMI: body mass index
BF: body fat
MS: metabolic syndrome
SNP: single nucleotide polymorphisms
UCP2: uncoupling protein 2
GIIS: glucose induced insulin secretion

LCPUFA: long chain polyunsaturated fatty acid

n-6 LCPUFAs
linoleic acid (C18:2n-6, LA)
gamma-linolenic acid (C18:3n-6, GLA)
eicosadienoic acid (C20:2n-6)
dihomo-gamma-linolenic acid (C20:3n-6, DHGLA)
arachidonic acid (C20:4n-6, AA)

n-3 LCPUFAs
alpha-linolenic acid (C18:3n-3, ALA)
eicosapentaenoic acid (C20:5n-3, EPA)
docosapentaenoic acid (C22:5n-3)
docosahexaenoic acid (C22:6n-3, DHA)

Introduction

Obesity has become an epidemic in many parts of the world, according to numerous studies conducted in adults and in the much limited data collected from young people. In Hungary, the prevalence of obesity increased from 12% to 16% between 1980' and 1990's among schoolchildren. Obesity results from the interaction of environmental factors (inappropriate eating behaviours and/or reduction in physical activity) and hereditary factors. According to several studies, 30 to 80% of weight variation might be determined by genetic factors. Genetic association studies in young people are important in that the influence of behavioural and exogenous factors are less marked than in adults, leaving a larger share to the SNPs to affect the phenotype. The number of genetic association studies has grown exponentially over the past 15 years, which was paralleled by a vast increase in the number of candidate genes. The ***CD36* gene** and the **uncoupling protein 2 (*UCP2*) gene** are one of the promising candidate genes for obesity. CD36 is a membrane receptor with wide variety of functions, including the regulation of energy metabolism, fat storage and adipocyte differentiation. We hypothesised that genetic variability at the CD36 gene locus might influence body fat deposition in adolescents. The effect of *UCP2* on obesity can be due to its suspected function in energy metabolism. UCP2 might enhance the proton leak, induce respiratory uncoupling, thereby releasing the energy stored within the proton motive force as heat, and resulting in a decrease in ATP synthesis. Recently, an association between obesity, lipid metabolism disorders and the G-allele of the -866G/A polymorphism in the promoter region of uncoupling protein 2 gene (UCP2) was reported.

Several environmental factors affect the obesity phenomenon significantly. Evidence has accumulated showing that early nutrition programs later obesity risk. The mechanisms involved are poorly understood, beside the role of several nutrients, **LCPUFAs (long chain polyunsaturated fatty acids**) may also play a significant role. LCPUFAs are fatty acids with a minimum chain length of 18 carbons containing at least 2 double bonds. Essential fatty acids can not be synthesised by humans and must be supplied through placental transport to the fetus and with human milk or milk substitute formulae to the infant. Preterm infants represent a small (about 5% to 10%), but highly vulnerable subgroup of infants. Optimal nutrition of preterm infants, including the prevention of obesity, is of obvious importance from the point of view of the health of the community. However, solid information of the

composition of human milk of mothers of preterm infants is a prerequiste of the optimisation of the composition of formulae to be used in the nutrition of premature babies.

Overweight and obesity in youth plays a central role in the **metabolic syndrome** (MS) - defined as a clustering of insulin resistance/hyperinsulinemia, dyslipidemia and hypertension. The process of atherosclerosis starts at an early age and is linked to obesity and other components of the metabolic syndrome in childhood. For these reasons, the recognition of MS in obese children, who have not yet developed cardiovascular disease, is of great importance from a clinical and public health perspective. A recent publication estimated the prevalence of MS in Europe on the basis of data obtained from a literature search and extrapolated them to the 25 member states. Most of the studies (n=6) used for the calculation of weighted average prevalence were performed on US children and only one was European

The presence of multiple metabolic disorders persists from childhood into adulthood 25%–60% of the time. The alarming increases in obesity in developing countries has led the World Health Organization to estimate that cardiovascular disease CVD will rise from number 5 to number 1, the leading killer in the entire world after another decade.

For all these reasons, CVD is and will remain the leading killer in the most developed countries. Thus, the long-term consequences of childhood obesity could cause our current generation of children to become the first in the history to have a decreased life expectancy than their parents.

Aims of the study

1. **Association among single nucleotide polymorphisms at CD36 locus and obesity in European adolescents**

a.) To explore the relationship between polymorphisms in the CD36 gene and obesity in a case-control study of adolescents.

b.) To validate our findings on anthropometric markers of obesity in an independent cross sectional study of European adolescents.

2. **Association of n-6 long-chain polyunsaturated fatty acids to -866G/A genotypes of the human uncoupling protein 2 gene in obese children**

a.) To examine the effect of −866 G/A polymorphism of UCP2 on the fatty acid composition of plasma lipids in obese children.

b.) To investigate the association of n-6 long-chain polyunsaturated fatty acids (LCPUFAs) with glucose-induced insulin secretion (GIIS) in obese children stratified according to the −866 G/A polymorphism of UCP2.

3. **Systematic review of fatty acid composition of human milk from mothers of preterm compared to full-term infants**

To systematically review the published information on fatty acid composition of human milk in mothers of preterm as compared to those of full-term infants.

4. **Prevalence of metabolic syndrome in European obese children**

a.) To review the data concerning the prevalence of metabolic syndrome in European children and adolescents.

b.) To determine and compare the prevalence of MS among overweight and obese children and adolescents in five European countries using four MS definitions.

1. Association among single nucleotide polymorphisms at CD36 locus and obesity in European adolescents

Patients and methods: We used two independent studies.

First, we evaluated the relationship between *CD36* SNPs and the risk of obesity in a case-control study. The study population consisted of 307 obese (age = 15.0±1.1 y) adolescents referred to the outpatient clinic of the Department of Pediatrics University of Pécs (Pécs, Hungary) for obesity and 339 healthy normal weight adolescents (age = 14.6 ±1.1 y) recruited via general schools of Pécs aged between 14-17 years. Obesity was defined as a BMI over the value given by Cole *et al.*

Then, to validate the results, we assessed the relation between the same SNPs and percentage of body fat (BF%) and BMI in European adolescents (age = 14.8±1.4 y) from the HELENA study. Briefly, a total of 3865 adolescents were recruited between 2006 and 2007. Data were collected in 10 centres from 9 European countries. One third of the cases were randomly selected for blood collection, resulting in a total of 1155 blood samples for the subsequent clinical biochemistry assays and genetic analyses.

The percentage of body fat was estimated from skinfold measurements according to the equations of Parizkova et al., and the BMI was calculated. With the criteria used in our SNP selection procedure (a minor allele frequency (MAF) above 0.1 and tag SNPs with an r^2 value above 0.8), the HapMap database (2007 release) describes 5 haplotype blocks and 2 independent SNPs that span the whole gene. In the present study, we selected 1 SNP from each of the five haplotype blocks (block 1: rs1527479, block 2: rs3211816, block 3: rs3211867, block 4: rs3211883 and block 5: rs3211931) and the two independent SNPs (rs3211908 and rs1527483). We also selected 3 other SNPs (rs1984112, rs1761667 and rs1049673) from the literature in order to cover the whole range of gene variability. Altogether, subjects were genotyped on an Illumina system, 1 SNP (rs1761667) using the VeraCode technology and the 9 other SNPs using GoldenGate technology. Statistical analyses were performed with SAS software (SAS Institute Inc., Cary, NC, USA).

Results: The genotyping success rate varied between 97.1 and 100%. Four SNPs (rs3211867, rs3211883, rs3211908 and rs1527483) were associated with increased risk of obesity in the case-control study (OR [95%CI]: 1.96 [1.26-3.04], p=0.003; 1.73 [1.16-2.59], p=0.007; 2.42 [1.47-4.01], p=0.0005 and 1.95 [1.25-3.05], p=0.003, respectively). Multivariate analyses (adjusted for age, gender and centre) revealed that the same 4 SNPs were consistently

associated with a higher BMI ($p<0.05$) and BF% ($p<0.04$) in the validation study. The mean BMI and BF% were significantly higher in carriers of at least one minor allele with rs3211867 (BMI: p=0.03, BF%: p=0.02), rs3211883 (BMI: p=0.03, BF%: p=0.05), rs3211908 (BMI: p=0.04, BF%: p=0.02) and rs1527483 (BMI: p=0.05, BF%: p=0.04) compared with individuals who were homozygous for the frequent allele.

Haplotype analyses using the 7 SNPs (order: rs1527479, rs3211816, rs3211867, rs3211883, rs3211908, rs3211931 and rs1527483) were performed to assess the relationship with obesity in the case-control study and the association with BMI and BF% in the HELENA-CSS. Nine haplotypes had an estimated frequency of over 1%. Compared with the most common haplotype (GGCTGGG; estimated frequency: 0.44), 1 haplotype: AGAAAAA (estimated frequency: 0.05, minor alleles underlined) was significantly associated with a higher risk of obesity (OR: 2.28 for obesity; p=0.0008). This haplotype was also associated with a higher BF% (p=0.03) and BMI (p=0.04) in the cross-sectional study.

Conclusion: Our data suggest that genetic variability at the CD36 gene locus is associated with body weight variability in European adolescents.

2. Association of n-6 long-chain polyunsaturated fatty acids to -866G/A genotypes of the human uncoupling protein 2 gene in obese children

Methods: The investigations were carried out in 80 obese children (age: 13.0 [2.7] (8.1 – 17.0) years, body mass index: 41.7 [4.4] (27.3 – 49.7) kg/m^2, body fat: 39.1 [4.2] (31.6 – 56.1) %, mean [SD] (min. – max.)) referred to the Outpatient Clinic for Obesity of the Department of Paediatrics, University of Pécs (Pécs, Hungary) because of their overweight. The OGTT consisted of oral administration of glucose (1.75 g/kg body weight, maximum 75 g) followed by plasma glucose and insulin determinations at 30, 60, 90, 120, and 180 min. Genomic DNA was extracted from peripheral blood leukocytes according to standard procedures. The -866 G/A polymorphism in the promoter region of the human UCP2 gene was investigated with polymerase chain reaction (PCR) and subsequent diagnostic restriction fragment length polymorphism analyses (RFLP) with the restriction enzyme Bsh1236I which either cut (-866 G-allele) or did not cut (-866 A-allele) the 201 basepair (bp) PCR amplicon. Fatty acids were analysed by high-resolution capillary gas-liquid chromatography using a Finnigan 9001 gas chromatograph (Finnigan/Tremetrics Inc., Austin, TX, USA) with split injection (ratio: 1 to 25), automatic sampler (A200SE, CTC Analytic, Switzerland) and flame-ionisation detector with a DB-23 cyanopropyl column of 40m length (J &W Scientific, Folsom, CA, USA).

Results: Values of dihomo-γ-linolenic acid (C20:3n-6) were significantly lower in children with the −866 A/A (n = 12) than in those with the −866 G/A (n = 34) or −866 G/G (n = 34) genotype in plasma phospholipids (3.01 [0.42] vs. 3.56 [1.02] vs. 3.53 [0.84], % weight/weight, median [interquartile range], $p < 0.05$), and were significantly lower in children with the −866 A/A genotype than in the other two groups in plasma sterol esters (0.73 [0.22] vs. 0.92 [0.23] vs. 0.94 [0.25], $p < 0.05$).

Phospholipid C20:3n-6 and arachidonic acid (C20:4n-6) values showed only in children with the −866 G/G and −866 G/A genotypes significant positive correlations with plasma insulin concentrations. Significant inverse correlation was seen in children with the −866 A/A genotype between C20:4n-6 and the insulin area under the curve, whereas no such correlation was observed in other groups.

Conclusions: Significantly lower values of C20:3n-6 can be detected in obese children with the homozygous (−866 A/A) mutation of UCP2 than in equally obese children with heterozygous mutation or the normal genotype. High glucose-stimulated insulin response is associated with high plasma C20:3n-6 and C20:4n-6 values only in obese children with the G allele of the −866 G/A polymorphism.

3. **Systematic review of fatty acid composition of human milk from mothers of preterm compared to full-term infants**

Methods: We performed an electronic literature search in English (Medline (www.pubmed.com) and Medscape (www.medscape.com)) and German (SpringerLink (www.springerlink.com)) databases from their start dates to November 2005 onwards. The searching expressions were as follows: human milk or breast milk, combined with essential fatty acid or long-chain polyunsaturated fatty acid or arachidonic acid or docosahexanoic acid. Data published were converted to differences between means and 95% CIs.

Results: We identified five relevant studies (1: Bitman, Am J Clin Nutr, 1983; 2: Luukkainen, J Pediatr Gastroenterol Nutr, 1994; 3. Genzel-Boroviczeny, Eur J Pediatr, 1997; 4: Rueda, Ann Nutr Metab, 1998; 5: Kovács, J Pediatr Gastroenterol Nutr, 2005) publishing direct comparison of fatty acid composition of preterm versus full-term human milk. There were no significant differences between the values of principal saturated and monounsaturated fatty acids. Values of LA, ALA and EPA did not differ between preterm and full-term human milk in any of the five studies.

In three independent studies covering three different time points of lactation, however, docosahexaenoic acid (DHA) values were significantly higher in milk of mothers of preterm as compared to those of full-term infants, with an extent of difference considered nutritionally relevant. (Table).

Table: Differences between means (preterm minus full-term) and 95% confidence intervals in 3 studies on human milk (* = significant difference)

Source (Ref. no.)	Age (day)	Arachidonic acid Difference (95% CI)	Docosahexaenoic acid Difference (95% CI)
2	182-189	0.09 (0.19, -0.01)	0.21 (0.35, 0.07)*
4	16-35	-0.20 (-0.10, -0.29)*	0.36 (0.55, 0.17)*
5	4	0.24 (0.45, 0.03)*	0.09 (0.22, -0.02)
5	7	0.33 (0.51, 0.14)*	0.15 (0.05, 0.26)*
5	21	0.25 (0.42, 0.07)*	0.07 (0.14, -0.003)

Summary: In 3 studies covering 3 stages of lactation, docosahexaenoic acid values were consequently, considerably and significantly higher in milk of mothers of preterm as compared to those of full-term infants.

4. Prevalence of metabolic syndrome in European obese children

a) **Methods:** Electronic literature search was performed in English (Medline and Medscape) and German (Springerlink) databases and via the Google utility.

Results:

Only few studies investigated the prevalence of MS in European countries as a primary goal. The studies were performed in Middle and South part of Europe (Spain, Italy, France, Germany, and Hungary), and only one in the North (UK). Except of two studies, the investigations were performed only on overweight and obese children and adolescents with a small number of subjects included. The used definitions were either based on the adult definitions from WHO or NCEP, modified with children specific cut-offs, or previously published definitions used to define MS in children. A big variance in the prevalence of MS (8.5% to 50%) can be observed among the studies; however, the results are not comparable since the used definitions were different. A low degree of overlap among the different MS definitions is pointed out in two studies, where more definitions were used.

b) **Patients and methods**: In total, 1 241 European obese children from five different countries (France: n=283, Greece: n=145, Italy: n=274, Poland: n=90, and Hungary: n=449) were studied for MS according to the definition of Ferranti et al., the World Health Organisation, the National Cholesterol Education Program and the International Diabetes Federation. We used age- and sex-specific cut-off values for the diagnosis of high blood pressure and increased waist circumference.

Results: The prevalence of MS in the investigated cohort was 35.7%, 31.4%, 20.3%, and 16.4% according to the Ferranti, WHO, NCEP and IDF definitions, respectively. Only 6.3-8.8% of obese adolescents were free from any risk factors and the clustering of three risk factors or more was very high: 20.3-35.7% (depending on the type of definition). A total of 12.2% of children had MS and 55.8% were free from MS according to all four definitions. The prevalence of increased waist circumference was high (71.4%). Due to different cut off values the occurrence of low HDL levels varied according to definitions. We found, as expected, the highest prevalence of elevated triglyceride levels according to Ferranti et al. and of elevated fasting plasma glucose according to the definition of IDF because of the lower cut

off values applied for these risk factors. The prevalence of MS was not different between genders. The prevalence of MS was significantly influenced by the degree of obesity, characterised by BMI or waist circumference, but not by age.

Conclusions: The prevalence of MS is high among European obese children whatever criteria are used. There is an urgent need to achieve consensus concerning the definition of MS in adolescents and children.

New findings of the study

1. The results of the present study on the common single nucleotide polymorphism at CD36 locus showed that rs3211908, rs3211867, rs3211883 and rs1527483 SNPs were consistently associated with obesity and BF% in adolescents. Collectively, these findings suggest that *CD36* gene variability may contribute to the risk of body fat accumulation in adolescents.

2. In the present study we observed significant differences in the values of important n-6 LCPUFAs according to -866G/A genotypes of the human uncoupling protein 2 gene in obese children. Furthermore, by correlating the fatty acid levels with the insulin response and the values calculated for insulin area under the curve during OGTT we observed considerable differences in relations to -866 polymorphism of the UCP2.

3. In the present review, we identified 3 independent studies covering 3 different time points of lactation were the 95% CIs of the significant difference of mean DHA values (preterm minus full-term) were entirely in the positive range, i.e. the percentage contribution of DHA is higher in preterm than full-term milk.

4. The results showed the high prevalence of MS ranging from 16.4% to 35.7% in overweight and obese children referred to outpatient clinics. The prevalence of MS was highly dependent on the definition used. The accordance among the definitions was small, only 12.2% of investigated subjects had MS according to all 4 definitions.
Our results demonstrated that only 6.3-11.3% of overweight and obese children were free from any risk factors, and 17.3-35.7% had already more than 3 risk factors, underlining the fact that clustering of risk factors starts in childhood.

Clinical consequences of the study

1. Because the CD36 receptor is theoretically considered to play an important role in determining the susceptibility to the development of obesity, genetic characterisation of subgroups with actually increased risk of obesity may contribute to our better understanding of the link between receptor and clinical outcome.

2. The association between the availability of n-6 polyunsaturated fatty acids and glucose induced insulin secretion may open further opportunity to the dietary amelioration of metabolic consequences of obesity. The data obtained in the present study may provide some general messages for research on fatty acids in obesity as well. Controversial results seen in previous investigations on LCPUFAs in apparently similar groups of obese subjects may, at least in part, originate from the different genetic background including *UCP2* polymorphism.

3. Higher DHA values in preterm than in full-term human milk indicate a likely benefit of utilising own mother's milk for feeding preterm infants. Moreover, these data should lead to a reconsideration of the DHA levels in formulae for preterm infants, which currently tend to mimic DHA levels of full-term human milk and thus tend to differ from the fatty acid composition of human milk of mothers giving birth to preterm infants.

4. The prevalence of metabolic syndrome is high in European overweight and obese children referred to obesity centres, whatever definition is used. Overweight and obese children, especially those with high waist circumference, have to be screened for MS. An unified childhood-specific definition of MS is needed in order to gain comparable study results and to avoid the possibility of different diagnosis of the same individual depending on the country he/she lives in and on the criteria used.

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Publications in the topic of the thesis

Papers

1. Bokor Szilvia, Csernus Katalin, Erhardt Éva, Molnár Dénes, Decsi Tamás: Role of the -866 G/A polymorphism of the uncoupling protein 2 gene in the metabolic consequences of obesity. (Az uncoupling protein 2 gén -866 G/A polimorfizmusának szerepe az elhízás metabolikus szövődményeinek kialakulásában.) Gyermekorvos továbbképzés V/4: 268-271; 2006
2. Bokor Szilvia, Csernus Katalin, Erhardt Eva, Burus István, Molnár Dénes, Decsi Tamás: Association of n-6 long-chain polyunsaturated fatty acids to -866 G/A genotypes of the human uncoupling protein 2 gene in obese children. Acta Paediatrica 96(9):1350-4; 2007. **Impact factor: 1.411**
3. Szilvia Bokor, Berthold Koletzko, Tamás Decsi: Systematic review of fatty acid composition of human milk from mothers of preterm compared to full-term infants. Annals of Nutrition and Metabolism. Annals of Nutrition and Metabolism. 2007;51(6):550-6**. Impact factor: 1.831**
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Abstracts that can be cited in the issue of the thesis

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8. Bokor Szilvia, Berthold Koletzko, Decsi Tamás: Systematic rewiew of fatty acid composition of human milk in preterm and full-term infants. (Poster presentation) European Society for Paediatric Gastroenterology, Hepatology And Nutrition Dresden, Germany, June 7-10, 2006
9. Szilvia Bokor, Berthold Koletzko, Tamás Decsi: Systematic rewiew of fatty acid composition of human milk in preterm and full-term infants. (Az anyatej zsírsavösszetétele koraszülöttet és időre születet újszülöttet szült anyákban: szisztémás irodalmi áttekintés.) (*Poster presentation*) Congress of the Hungarian Pediatric Association (Magyar Gyermekorvosok Társasága 2006. évi Nagygyűlése) Siófok, Hungary, October 06-07, 2006

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