Insulin Resistance, the Metabolic Syndrome and Type 2 Diabetes

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Insulin resistance and related disorders have proven to be a matter of concern for pediatricians in recent years. This is reflected in a decision by the Editors to devote a chapter to this issue. Numerous papers are dedicated to the subject in the literature this year. The papers focus on the basic knowledge on the mechanisms of insulin resistance, which is not fully understood yet and we have kept the most significant or innovative paper in this respect. Numerous clinical studies are related to risk factors for insulin resistance and the metabolic syndrome in childhood. Papers which develop a specific aspect of pediatric care, and do not only replicate the studies performed in adults, have kept our attention as well as those with data directly transferable to clinical practice.

Mechanism of the year

Local and systemic insulin resistance resulting from hepatic activation of IKK- β and NF- κ B

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Nat Med 2005;11:183–190

Background: Obesity and insulin resistance are linked to a subacute inflammatory state. NF- κ B and transcriptional targets are activated in liver by obesity and high-fat diet.

Methods: Selective production of a state of chronic, subacute 'inflammation' in liver through transgenic expression of IKK- β constitutively activates IKK- β in hepatocytes inducing activation of NF- κ B.

Results: These mice exhibit a type 2 diabetes phenotype, characterized by hyperglycemia, profound hepatic insulin resistance, and moderate systemic insulin resistance, including effects in muscle. The hepatic production of proinflammatory cytokines, including IL-6, IL-1 β and TNF- α , was increased in the transgenic mice to a similar extent as induced by high-fat diet in wild-type mice. Parallel increases were observed in cytokine signaling in liver and muscle of transgenic mice. Insulin resistance was improved by systemic neutralization of IL-6 or salicylate inhibition of IKK- β . Hepatic expression of the I κ B α superrepressor (LISR) reversed the phenotype of both LIKK mice and wild-type mice fed a high-fat diet.

Conclusion: These findings indicate that lipid accumulation in the liver leads to subacute hepatic 'inflammation' through NF- κ B activation and causes profound hepatic insulin resistance and moderate systemic insulin resistance.

IKK- β links inflammation to obesity-induced insulin resistance

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Background: Inflammation may underlie the metabolic disorders of insulin resistance and type 2 diabetes. I κ B kinase β (IKK- β , encoded by *Ikkb*) is a central coordinator of inflammatory responses through activation of NF- κ B. To understand the role of IKK- β in insulin-regulated glucose metabolism, specific knock-out were used.

Methods: Conditional knockout of IKK- β in hepatocytes (*Ikkb*(Deltahep)) or myeloid cells (*Ikkb*(Deltamyel)).

Results: Ikkkb(Deltahep) mice retain liver insulin responsiveness, but develop insulin resistance in muscle and fat in response to high-fat diet, obesity or aging. In contrast, Ikkkb(Deltamye) mice retain global insulin sensitivity and are protected from insulin resistance. Thus, IKK- β acts locally in liver and systemically in myeloid cells, where NF- κ B activation induces inflammatory mediators that cause insulin resistance. These findings demonstrate the importance of liver cell IKK- β in hepatic insulin resistance and the central role of myeloid cells in development of systemic insulin resistance.

Conclusion: Inhibition of IKK- β , especially in myeloid cells, may be used to treat insulin resistance.

In the last two years we have learnt that obesity is in many ways a state of inflammation of the adipose tissue. By using overexpression or invalidation of a key enzyme in the production of the hepatic NF- κ B respectively, these two papers produce data establishing a molecular link between obesity-induced inflammation and insulin resistance. Although it is not clear how high-fat diet causes activation of NF- κ B and its target genes in liver cells, it is possible that excessive fatty acid oxidation in mitochondria generates peroxidation products that may initiate a signaling cascade that culminates in NF- κ B activation. Hepatic local inflammatory response is induced by IKK- β , which in turn produces cytokines, which enter the circulation and cause insulin resistance. Unraveling this mechanism is a major achievement and opens up future new ways of treating insulin resistance. These findings raise the possibility that susceptibility genes for type 2 diabetes may not lie in the pathways of insulin action, or even be expressed within traditional insulin target tissues.

New hormone

Visfatin: a protein secreted by visceral fat that mimics the effects of insulin

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Science 2005;307:426–430

Background: Fat tissue produces a variety of adipocytokines with important roles in metabolism.

Methods: Several in vitro and in vivo studies, including circulating concentrations in humans.

Results: Isolation of a newly identified adipocytokine, visfatin, that is highly enriched in the visceral fat of both humans and mice and whose expression level in plasma increases during the development of obesity. Visfatin corresponds to a protein identified previously as pre-B cell colony-enhancing factor (PBEF), a 52-kDa cytokine expressed in lymphocytes. Visfatin exerted insulin-mimetic effects in cultured cells and lowered plasma glucose levels in mice. Mice heterozygous for a targeted mutation in the visfatin gene had modestly higher levels of plasma glucose relative to wild-type littermates. Surprisingly, visfatin binds to and activates the insulin receptor.

Conclusion: Further study of visfatin's physiological role may lead to new insights into glucose homeostasis and/or new therapies for metabolic disorders such as diabetes.

This is a newly described and interesting hormone: for the first time a hormone other than insulin exists that is able to lower blood glucose! Visfatin is detected at picomolar levels in serum. Responses in glucose and lipid metabolism are also seen at picomolar concentrations. However, it remains to be seen in which system of regulation Visfatin could be integrated. It is only 4 years since resistin was introduced, then disappeared when we realized that it was a mouse hormone more than a human one. We will have to see if Visfatin stays with us longer.

Complementary roles of IRS-1 and IRS-2 in the hepatic regulation of metabolism

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J Clin Invest 2005;115:718–727

Background: Hepatic insulin resistance is a critical component in the development of type 2 diabetes mellitus. In many cases, insulin resistance in liver is associated with reduced expression of both major insulin receptor substrate (IRS) proteins, IRS-1 and IRS-2.

Aim: To investigate the specific functions of IRS-1 and IRS-2 in regulating liver function in vivo.

Methods: An adenovirus-mediated RNA interference technique used to knock down IRS-1, IRS-2, or both, in livers of *wt* mice.

Results: The knock down of IRS-1 resulted in an upregulation of the gluconeogenic enzymes glucose-6-phosphatase and phosphoenolpyruvate carboxykinase, as well as a marked increase in HNF-4 α . Decreased IRS-1 was also associated with a decrease in glucokinase expression and a trend toward increased blood glucose, whereas knock down of IRS-2 resulted in the upregulation of lipogenic enzymes SREBP-1c and fatty acid synthase, as well as increased hepatic lipid accumulation. The concomitant knock down of IRS-1 and IRS-2 resulted in systemic insulin resistance, glucose intolerance, and hepatic steatosis. The alterations in the dual knock down mice were associated with defective Akt activation and Foxo1 phosphorylation.

Conclusion: Taken together, these results demonstrate that hepatic IRS-1 and IRS-2 have complementary roles in the control of hepatic metabolism, with IRS-1 more closely linked to glucose homeostasis and IRS-2 more closely linked to lipid metabolism.

The results show distinct but complementary effects of IRS-1 and IRS-2 on insulin receptor downstream signals. IRS-1 is more involved in glucose metabolism and IRS-2 in lipid metabolism, and invalidation of both is necessary for insulin resistance to appear. This paper is of interest because of both the technological aspect and the new information about hepatic insulin resistance. The technology is very elegant, using siRNAs, which does not modify the gene itself but only and transiently its translation (RNA stability); it also allows for targeted invalidation of the effect of the gene in the liver without any permanent compensatory effects in the cells. Therefore, the physiological effects of either IRS-1 or IRS-2, or both, on hepatic insulin signaling can be individually distinguished (when the respective knockout animals did not) without the pleiotropic side effects that could occur in globally knockout animals.

New concept

Premature birth and later insulin resistance

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Background: Term infants who are small for gestational age appear prone to the development of insulin resistance during childhood. It was hypothesized that insulin resistance, a marker of type 2 diabetes mellitus, would be prevalent among children who had been born prematurely, irrespective of whether they were appropriate for gestational age or small for gestational age.

Methods: Seventy-two healthy prepubertal children 4–10 years of age were studied: 50 who had been born prematurely (32 weeks' gestation or less), including 38 with a birth weight that was appropriate for gestational age (above the 10th percentile) and 12 with a birth weight that was low (i.e., who were small) for gestational age, and 22 control subjects (at least 37 weeks' gestation, with a birth weight

above the 10th percentile). Insulin sensitivity was measured with the use of paired insulin and glucose data obtained by frequent measurements during intravenous glucose-tolerance tests.

Results: Children who had been born prematurely, whether their weight was appropriate or low for gestational age, had an isolated reduction in insulin sensitivity as compared with controls (appropriate-for-gestational-age group, 14.2×10^{-4} /min/mU/l (95% CI 11.5–16.2); small-for-gestational-age group, 12.9×10^{-4} /min/mU/l (95% CI 9.7–17.4), and control group, 21.6×10^{-4} /min/mU/l (95% CI 17.1–27.4; $p = 0.002$). There were no significant differences in insulin sensitivity between the two premature groups ($p = 0.80$). As compared with controls, both groups of premature children had a compensatory increase in acute insulin release (appropriate-for-gestational-age group, 2,002 pmol/l (95% CI 1,434–2,432); small-for-gestational-age group, 2,253 pmol/l (95% CI 1,622–3,128), and control group, 1,148 pmol/l (95% CI 875–1,500; $p < 0.001$).

Conclusions: Like children who were born at term but who were small for gestational age, children who were born prematurely had an isolated reduction in insulin sensitivity, which may be a risk factor for type 2 diabetes mellitus.

This paper extends the concept of fetal programming of insulin resistance to prematurity. In fact, very young premies have an initial growth arrest, which makes them 'SGA' at term. In this study, premies exhibit insulin resistance at a prepubertal age whether they were born SGA or AGA. The lack of an additional effect of SGA in this situation is not firmly established because of potential biases in the study groups (the full-term SGA group in this study is made up of a historical group of SGA children with short stature; the recall of the premature babies is largely incomplete). We still have to elucidate the respective roles of growth restriction occurring during the intrauterine vs. extrauterine (until full term) life. Nevertheless, children born premature are now to be considered at increased risk of metabolic syndrome, similarly to those born SGA at term.

Concept revised

Dynamic change in adiposity from fetal to postnatal life is involved in the metabolic syndrome associated with reduced fetal growth

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Diabetologia 2005;48:849–855

Aims: The aims of this study were to establish the role of insulin resistance in the metabolic syndrome associated with restricted fetal growth and to characterize the fetal and postnatal determinants responsible for the long-term metabolic outcome.

Methods: The study population consisted of adults selected on birth data from a maternity registry and born either small for gestational age (SGA) ($n = 734$, birth weight <10 th percentile) or appropriate for gestational age (AGA) ($n = 886$, 25th $<$ birth weight <75 th percentile) and in whom clinical and metabolic parameters of the metabolic syndrome were measured at 22 years of age.

Results: Mean values of all components of the metabolic syndrome significantly differed between the two groups, with the metabolic syndrome observed in 2.3% of the SGA group and in 4 per thousand of the AGA group ($p = 0.0004$). In SGA subjects, the upper tertile of fasting insulinemia was associated with the highest values of systolic ($p = 0.001$) and diastolic ($p = 0.02$) blood pressure, triglyceridemia ($p = 0.005$) and glycemia at fasting ($p = 0.0001$) and during OGTT ($p = 0.0001$). In SGA subjects, insulin resistance was not related to birth weight itself ($p = 0.26$), but correlated negatively with BMI at birth ($p = 0.03$) and positively with the subsequent postnatal catch-up in BMI ($p = 0.009$).

Conclusion: Insulin resistance is the keystone of metabolic syndrome associated with SGA, and its origin should be sought in the fetal development process of adiposity that is responsible for postnatal growth and the later development of insulin resistance.

Redistribution of glucose from skeletal muscle to adipose tissue during catch-up fat: a link between catch-up growth and later metabolic syndrome

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Diabetes 2005;54:751–756

Background: Catch-up growth, a risk factor for later obesity, type 2 diabetes, and cardiovascular diseases, is characterized by hyperinsulinemia and an accelerated rate for recovering fat mass, i.e., catch-up fat.

Aim: To identify potential mechanisms in the link between hyperinsulinemia and catch-up fat during catch-up growth, the authors studied the in vivo action of insulin on glucose utilization in skeletal muscle and adipose tissue in a previously described rat model of weight recovery exhibiting catch-up fat caused by suppressed thermogenesis per se. Euglycemic-hyperinsulinemic clamps associated with the labeled 2-deoxyglucose technique were used.

Results: After 1 week of isocaloric refeeding, when body fat, circulating free fatty acids, or intramyocellular lipids in refed animals had not yet exceeded those of controls, insulin-stimulated glucose utilization in refed animals was lower in skeletal muscles (by 20–43%) but higher in white adipose tissues (by 2- to 3-fold). Furthermore, fatty acid synthase activity was higher in adipose tissues from refed animals than from fed controls.

Conclusion: Suppressed thermogenesis for the purpose of sparing glucose for catch-up fat, via the coordinated induction of skeletal muscle insulin resistance and adipose tissue insulin hyperresponsiveness, might be a central event in the link between catch-up growth, hyperinsulinemia and risks for later metabolic syndrome.

In this cohort study, we confirmed that children born SGA are at increased risk for developing the metabolic syndrome, as compared to those born AGA. More importantly, we established that those who catch up are at even a higher risk for the metabolic syndrome. Catch-up growth has been incriminated by epidemiological data in the development of insulin resistance in SGA. It is indeed not the catch-up growth in height but in adiposity that is involved in this process. Moreover, catch-up occurs not because of a low birth weight but because of deleterious growth restriction; catch-up is seen in this condition as a post-natal compensatory phenomenon to a fetal insult. It is therefore reminiscent of what occurs during catch-up following wasting. The second paper using a very elegant animal model shows how and where insulin resistance develops. Additional relevant references are cited at the end of the chapter [1–4]. This new concept has several theoretical and practical consequences. First, epidemiological data derived from observations of cohorts of SGA children do not necessarily apply to those who do not catch up and who are seen in priority by pediatric endocrinologists. Second, the concept of first year variation in weight might not be restricted to SGA babies but might extend to other groups as well.

Lack of support for a role of the insulin gene variable number of tandem repeats minisatellite (INS-VNTR) locus in fetal growth or type 2 diabetes-related intermediate traits in United Kingdom populations

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J Clin Endocrinol Metab 2004;89:310–317

Background: The insulin gene variable number of tandem repeats minisatellite (INS-VNTR) class III allele is associated with altered fetal growth, type 2 diabetes risk (especially when paternally inherited), and insulin and IGF2 gene expression. Further studies are needed to establish the role of the INS-VNTR in fetal growth and assess whether its effects depend on the parent of origin.

Methods: The INS-VNTR-linked -23 Hph1 polymorphism was analyzed in 2,283 subjects, comprising 1,184 children and 1,099 parents.

Results: There were no differences ($p < 0.05$) in birth weight between offspring of the three genotypes: III/III ($n = 108$) vs. I/I ($n = 558$), effect size, -8 g ($p = 0.87$), and I/III ($n = 464$) vs. I/I, effect size,

−19 g ($p = 0.54$). No differences were observed in head circumference [III/III ($n = 95$) vs. I/I ($n = 470$), effect size, −0.14 cm; $p = 0.31$] or birth length. No differences were observed when stratifying by post-natal growth realignments [non-changers III/III ($n = 37$) vs. I/I ($n = 170$), effect size, −43 g; $p = 1.00$] or by parent of origin of the class III allele (presence of paternal III allele effect size, −15 g; $p = 0.74$). INS-VNTR was nominally associated ($p < 0.05$) with body mass index and insulin resistance, but not with β -cell function, in young adults.

Conclusion: In the largest study to date, a lack of support was found for a role for INS-VNTR in fetal growth and nominal association with type 2 diabetes-related intermediate traits.

The insulin VNTR polymorphism is associated with a $\approx 20\%$ variation of insulin levels and has been extensively studied for its association with susceptibility to type 1 and type 2 diabetes, birth weight, obesity risk . . . This study confirms the difficulty of confirming relatively weak genetic associations in different samples of individuals. The first publication involving the insulin VNTR and birth weight was by Dunger et al. [5], who showed an association between the class I allele and decreased birth weight in a subset of subjects with low birth weight. This association with birth weight was later confirmed in Pima Indians but not in patients with type 2 diabetes [6]. Here the association is not confirmed in an independent British birth cohort, similarly to the findings in the Finnish birth cohort [7, 8]. Likewise, our group studied the association of the insulin VNTR polymorphism and birth characteristics or metabolic data and we did not replicate previous findings [9]. Altogether, this information indicates that the contribution of the insulin gene VNTR polymorphisms studied are not strongly associated with the phenotypes observed. It should be kept in mind however, that classifying the VNTR alleles to class I and class III is probably an oversimplification.

New concern

Nature and nurture, the two arms of the metabolic syndrome

The metabolic syndrome in overweight Hispanic youth and the role of insulin sensitivity

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J Clin Endocrinol Metab 2004;89:108–113

Background: It is well known that the prevalence of the metabolic syndrome highly varies with ethnicity in adults the USA. The metabolic syndrome is strongly linked to insulin resistance. Such information is lacking in children.

Methods: Subjects were 126 overweight children (8–13 years of age) with a family history for type 2 diabetes. The metabolic syndrome was defined as having at least three of the following: abdominal obesity, low high-density lipoprotein (HDL) cholesterol, hypertriglyceridemia, hypertension, and/or impaired glucose tolerance. Insulin sensitivity was determined using the minimal model.

Results: The prevalence of abdominal obesity, low HDL cholesterol, hypertriglyceridemia, systolic and diastolic hypertension, and impaired glucose tolerance was 62, 67, 26, 22, 4, and 27%, respectively. The presence of zero, one, two, or three or more features of the metabolic syndrome was 9, 22, 38, and 30%, respectively. After controlling for body composition, insulin sensitivity was positively related to HDL cholesterol ($p < 0.01$) and negatively related to triglycerides ($p < 0.001$) and systolic ($p < 0.01$) and diastolic blood pressure ($p < 0.05$). Insulin sensitivity significantly decreased ($p < 0.001$) as the number of features of the metabolic syndrome increased.

Conclusion: Overweight Hispanic youth with a family history for type 2 diabetes are at increased risk for cardiovascular disease and type 2 diabetes, and this appears to be due to decreased insulin sensitivity.

Insulin resistance and cardiovascular disease risk factors in children of parents with the insulin resistance (metabolic) syndrome

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Diabetes Care 2004;27:775–780

Aim: To evaluate whether children of parents with the insulin resistance syndrome themselves have greater insulin resistance and unfavorable patterns of cardiovascular disease risk factors.

Methods: This cross-sectional study included 220 white and 36 black children aged 11–15 years identified through a school-based blood pressure screening program, along with 378 of their parents. Measures of insulin resistance (using euglycemic-hyperinsulinemic clamp), adiposity, and other cardiovascular disease risk factors were compared in children with and without a parental history of insulin resistance syndrome.

Results: Compared with children in whom neither parent had insulin resistance syndrome, children who had at least one parent with the syndrome had statistically significantly lower mean glucose disposal (12.1 vs. $13.6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; $p = 0.04$) and higher fasting insulin (geometric means 99 vs. 76 pmol/l ; $p = 0.01$) after adjustment for sex, race, age, and Tanner stage. Mean BMI, waist circumference, waist-to-hip ratio, triceps and subscapular skinfolds, and percentage of body fat were also significantly higher in children of an affected parent, but there were no significant differences in lipid or blood pressure levels between the two groups.

Conclusion: Insulin resistance and obesity may be the earliest manifestations of insulin resistance syndrome in children with a parental history of the syndrome.

These two studies emphasize the role of genetic factors in the development of the metabolic syndrome in childhood and adolescence. The study by Cruz et al. is based on Hispanic children with at least two important risk factors for type 2 diabetes and the metabolic syndrome (family history and ethnicity). Approximately 90% of overweight Hispanic children with a family history for type 2 diabetes have at least one feature of the metabolic syndrome and 30% have the metabolic syndrome. This could explain the high prevalence of the metabolic syndrome.

The study by Pankow et al. is an impressive achievement since euglycemic clamps were performed in about 400 children from the general population. This excellent work has provided [10–13] and provides useful and well-documented data on insulin resistance, metabolic syndrome and related parameters in adolescence. The study emphasizes the critical role of parental history of metabolic syndrome in determining the risk in offspring. Children with at least one affected parent showed increased insulin resistance and adiposity (both extent and distribution of adiposity). The effect was weaker on lipids and BP, at least in this age group.

Altogether, the data emphasize the key role of insulin resistance in the metabolic complications of overweight and obesity, identifiable in children as well as in adults. Populations with a high risk for metabolic complications and relevant for screening can therefore be identified. The practical consequences have to be discussed at length: should we focus intervention or metabolic screening on those who are genetically at higher risk of developing components of the metabolic syndrome?

First UK survey of paediatric type 2 diabetes and MODY

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Arch Dis Child 2004;89:526–529

Aim: To estimate the UK prevalence of childhood type 2 diabetes and maturity-onset diabetes of the young (MODY), and distinguish them from each other and from type 1 diabetes.

Methods: The British Society for Paediatric Endocrinology and Diabetes Clinical Trials/Audit Group undertook a cross-sectional questionnaire survey of all paediatric diabetes centres during 2000, collecting data on all children with non-type 1 diabetes.

Results: Of 112 children reported to the survey, 25 had type 2 diabetes and 20 had MODY. In contrast to type 1, type 2 patients presented later (12.8 vs. 9.3 years), were usually female, overweight, or obese

(92 vs. 28%), and a greater proportion were of ethnic minority origin (56 vs. 22%). In contrast to type 2, MODY patients were younger (10.8 years), less likely to be overweight or obese (50 vs. 92%), and none were from ethnic minority groups. The crude minimum UK prevalence of type 2 diabetes under 16 years is 0.21/100,000, and of MODY is 0.17/100,000. South-Asian children have a relative risk of type 2 diabetes of 13.7 compared to white UK children.

Conclusions: UK children still have a low prevalence of type 2 diabetes. Children from ethnic minorities are at significantly higher risk, but in white UK children with non-type 1 diabetes a diagnosis of MODY is as likely as type 2 diabetes. Childhood type 2 diabetes is characterized by insulin resistance, and is distinct from both type 1 and MODY.

This study is important because it is the first on epidemiology of non-type 1 diabetes in a population-based cohort of children; it is the first therefore to provide population data to quantify the magnitude of the type 2 diabetes phenomenon in European children. It emphasizes that type 2 diabetes has not reached high rates in the UK and that MODYs are not rare diseases. Such epidemiological surveys on type 2 diabetes would be of interest in other countries and on an ongoing basis for the next decade. It reminds us as clinicians that hyperglycemia is not just diabetes, but a variety of conditions leading to the failure of glucose homeostasis.

Youth type 2 diabetes: insulin resistance, β -cell failure, or both?

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Diabetes Care 2005;28:638–644

Aim: Evaluation of insulin sensitivity, pancreatic β -cell function, and the balance between the two in youth with type 2 diabetes and assessment of the relationship of diabetes duration and HbA(1c) to insulin sensitivity and β -cell function.

Methods: 14 adolescents with type 2 diabetes were compared to 20 obese control subjects of same age, BMI, body composition, and puberty. Insulin sensitivity was evaluated with a 3-hour hyperinsulinemic euglycemic clamp. First-phase insulin secretion (FPIS) and second-phase insulin secretion (SPIS) were evaluated with a 2-hour hyperglycemic (12.5 mmol/l) clamp.

Results: Insulin sensitivity was lower in type 2 diabetic patients than in obese control subjects (1.0 ± 0.1 vs. $2.0 \pm 0.2 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}/\text{pmol/l}$; $p = 0.001$). Fasting insulin was higher in type 2 diabetic patients than in obese control subjects (289.8 ± 24.6 vs. $220.2 \pm 18.0 \text{ pmol/l}$; $p = 0.007$), and FPIS and SPIS were lower (FPIS: 357.6 ± 42.0 vs. $1,365.0 \pm 111.0 \text{ pmol/l}$; SPIS: 652.2 ± 88.8 vs. $1,376.4 \pm 88.8 \text{ pmol/l}$; $p < 0.001$ for both). The glucose disposition index (GDI = insulin sensitivity $\times$ FPIS) was approximately 86% lower in type 2 diabetic patients than in obese control subjects. HbA(1c) correlated with FPIS ($r = -0.61$, $p = 0.025$) with no relationship to insulin sensitivity.

Conclusion: Despite the impairment in both insulin sensitivity and β -cell function in youth with type 2 diabetes, the magnitude of the derangement is greater for β -cell function than for insulin sensitivity, in comparison with non-diabetic obese subjects. The inverse relationship between β -cell function and HbA(1c) may either reflect the impact of deteriorating β -cell function on glycemic control or be a manifestation of a glucotoxic phenomenon on β -cell function. Future studies in youth type 2 diabetes should target the natural course of β -cell failure and means of retarding and/or preventing it.

This is the first study in youth demonstrating that both insulin sensitivity and insulin secretion are impaired in adolescents with type 2 diabetes. The impairment in β -cell function appears to be of greater magnitude relative to that of insulin sensitivity. It emphasizes the critical role of the impairment of insulin secretion in the clinical development of type 2 diabetes in adolescents. Given the age of occurrence of the disease (adolescence) it is very likely that insulin secretion deteriorates at a very fast rate (more rapidly than in adults) in obese adolescents susceptible to the disease. This hypothesis deserves careful prospective studies. Indeed identifying those who are 'rapid' progressors would have important therapeutic implications.

The prevalence and magnitude of childhood obesity are increasing dramatically in both the USA and Europe. Recent studies have reported an increased prevalence of type 2 diabetes in obese children and adolescents, especially in specific ethnic subgroups. Other risk factors for the metabolic complications are well established in adults, but data are lacking in children. To increase the efficiency of screening in the pediatric population we need to identify more precisely these risk factors, especially in Europe, and to establish a valid definition of the metabolic syndrome. The five following papers deal with these issues.

Obesity and the metabolic syndrome in children and adolescents

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N Engl J Med 2004;350:2362–2374

Aim: To test for the effect of varying degrees of obesity on the prevalence of the metabolic syndrome and its relation to insulin resistance and to C-reactive protein and adiponectin levels in a large, multiethnic, multiracial cohort of children and adolescents.

Methods: A standard glucose-tolerance test was administered to 439 obese, 31 overweight, and 20 non-obese children and adolescents. Baseline measurements included blood pressure and plasma lipid, C-reactive protein, and adiponectin levels. Levels of triglycerides, high-density lipoprotein cholesterol, and blood pressure were adjusted for age and sex. Because the body mass index varies according to age, the value was standardized for age and sex with the use of conversion to a z-score.

Results: The prevalence of the metabolic syndrome increased with the severity of obesity and reached 50% in severely obese youngsters. Each half-unit increase in the body mass index, converted to a z-score, was associated with an increase in the risk of the metabolic syndrome among overweight and obese subjects (OR 1.55, 95% CI 1.16–2.08), as was each unit of increase in insulin resistance as assessed with the homeostatic model (OR 1.12, 95% CI 1.07–1.18 for each additional unit of insulin resistance). The prevalence of the metabolic syndrome increased significantly with increasing insulin resistance (*p* for trend, <0.001) after adjustment for race or ethnic group and the degree of obesity. C-reactive protein levels increased and adiponectin levels decreased with increasing obesity.

Conclusions: The prevalence of the metabolic syndrome is high among obese children and adolescents, and it increases with worsening obesity. Biomarkers of an increased risk of adverse cardiovascular outcomes are already present in these youngsters.

Prevalence of the insulin resistance syndrome in obesity

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Arch Dis Child 2005;90:10–14

Aims: To assess prevalence of the insulin resistance syndrome (obesity, abnormal glucose homeostasis, dyslipidaemia, and hypertension) in obese UK children and adolescents of different ethnicities and to assess whether fasting data is sufficient to identify insulin resistance syndrome in childhood obesity.

Methods: A total of 103 obese (BMI > 95th centile) children and adolescents 2–18 years of age referred for assessment underwent an oral glucose tolerance test, measurement of fasting lipids, and blood pressure determination. Main outcome measures were prevalence of components of insulin resistance syndrome by modified WHO criteria, with insulin resistance syndrome defined as ≥ 3 components (including obesity).

Results: There were 67 girls (65%). BMI z-score ranged from 1.65 to 6.15, with 72% having a z-score ≥ 3.0 . Abnormal glucose homeostasis was identified in 46% (hyperinsulinism in 40%, impaired

fasting glucose in 0.8%, impaired glucose tolerance in 11%). No subjects had silent type 2 diabetes. Dyslipidaemia was identified in 30% and hypertension in 32%. 31% had obesity alone, 36% had two components, 28% had three, and 5% had all four components. Birth weight, BMI, and family history of insulin resistance syndrome were not associated with risk of insulin resistance syndrome. Higher age increased the risk of insulin resistance syndrome, however the syndrome was seen in 30% of children <12 years. The use of fasting glucose and insulin data for identifying insulin resistance syndrome had a sensitivity of 88% and specificity of 100%.

Conclusions: One-third of obese children and adolescents have the insulin resistance syndrome, however type 2 diabetes is rare. Obese children with the insulin resistance syndrome may form a high-risk group to whom scarce intervention resources should be targeted. Further work is needed to develop appropriate screening programs for insulin resistance syndrome components in significantly obese children.

Clinical characteristics of type 2 diabetes mellitus in overweight European Caucasian adolescents

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Aim: To present the clinical features of type 2 diabetes mellitus in overweight European Caucasian children and adolescents.

Methods: Clinical characteristics of 16 non-syndromal overweight European Caucasian adolescents with type 2 diabetes (10 boys, 6 girls, SDS-BMI in median +2.8, range +1.6 to +3.4) treated in 5 specialised centres for obesity and diabetes.

Results: None of the adolescents manifested with ketoacidosis. 13 were asymptomatic (3 adolescents with polyuria), 12 showed features of metabolic syndrome (dyslipidaemia or hypertension), 8 demonstrated acanthosis nigricans and 12 had relatives with type 2 diabetes. 11 adolescents were extremely obese and all patients were pubertal. Mean age at diagnosis was 14.2 years (range 11.0–16.9). Median insulin was 19 μ U/ml, insulin resistance index (HOMA) 8.5, C-peptide 2.3 ng/ml, HbA1c 6.9%, fasting blood glucose 176 mg/dl and blood glucose at 2 h with the OGTT 229 mg/dl at manifestation. Fasting blood glucose and HbA1c were in the normal range in 4 and 6 adolescents respectively, while OGTT always fitted the diagnosis of type 2 diabetes mellitus.

Conclusion: Since type 2 diabetes occurred in Caucasian overweight adolescents and is frequently asymptomatic, it is essential that clinicians perform diagnostic procedures to identify type 2 diabetes in high-risk groups of overweight Caucasian adolescents (extreme obesity, features of metabolic syndrome, relatives with type 2 diabetes).

Type 2 diabetes mellitus and impaired glucose regulation in Caucasian children and adolescents with obesity living in Germany

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Aim: To determine the prevalence of type 2 diabetes mellitus and impaired glucose regulation in a large group of Caucasian children and adolescents with obesity living in Germany.

Methods: A total of 520 subjects (237 boys, 283 girls) (mean age 14.0 ± 2.0 years (range 8.9–20.4)) with a BMI > 97th percentile, BMI-SDS 2.7 ± 0.5 (range 1.9–4.6), who were consecutively admitted to an inpatient obesity unit participated in the study. A 2-hour oral glucose tolerance test (1.75 mg glucose/kg body weight) was performed before entering a weight-loss program and capillary blood glucose concentrations were measured. Patients were categorized into normal glucose regulation, impaired fasting glucose, impaired glucose tolerance and diabetes. In addition, fasting venous blood was taken to determine the circulating insulin, C-peptide and lipids. Insulin resistance was estimated by homeostatic model assessment.

Results: Type 2 diabetes was present in 1.5% ($n = 8$) of the patients, 2 patients were admitted with already diagnosed type 2 diabetes, and 6 patients were identified with yet unknown diabetes. Impaired fasting glucose was detected in 3.7% ($n = 19$) and impaired glucose tolerance in 2.1% ($n = 11$) of the patients. Altogether, in 6.7% ($n = 35$) (95% CI 4.7–9.2%) of the patients, impaired glucose regulation or diabetes was identified. These patients had a higher BMI-SDS, higher levels of fasting insulin and C-peptide and a higher insulin resistance index than the patients with normal glucose regulation. Risk factors for the occurrence of impaired glucose regulation were a BMI-SDS >2.5 as well as a positive parents' history for diabetes.

Conclusions: This is the first report on the prevalence of type 2 diabetes in a large cohort of Caucasian children and adolescents with obesity living in Europe. Impaired glucose regulation and type 2 diabetes were present in a substantial proportion of the patients studied. Screening for diabetes in severely obese children and adolescents (BMI-SDS > 2.5) is therefore recommended.

Type 2 diabetes and impaired glucose tolerance in European children and adolescents with obesity – a problem that is no longer restricted to minority groups

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Background: The incidence of childhood obesity and type 2 diabetes is an increasing problem in Europe. The prevalence of impaired glucose regulation was determined in a predominantly Caucasian cohort of 491 children and adolescents with obesity.

Methods: Fasting glucose and insulin levels were determined in all 491 subjects. Patients with an abnormal fasting glucose or with additional risk factors (positive family history of type 2 diabetes, acanthosis nigricans, hyperlipidemia; $n = 102$) underwent an oral glucose tolerance test (OGTT; 1.75 g glucose/kg body weight). Homeostasis model assessment was used to estimate insulin resistance in all subjects. The insulin sensitivity index was determined in those subjects who underwent an OGTT. Screening for mutations in the melanocortin 4 receptor (MC4R) gene and the coding region of the brain-derived neurotrophic factor (BDNF) in 37 patients with an impaired glucose tolerance was performed by WAVE analysis.

Results: Out of the total of 491 patients, 12 had an abnormal fasting glucose level. Of the 102 patients who underwent an OGTT, 37 had impaired glucose tolerance; 6 out of the 102 patients were diagnosed with type 2 diabetes. 88% of patients with abnormal glucose tolerance and 66% of patients with type 2 diabetes were Caucasian. Insulin resistance indices correlated well with the degree of abnormal glucose tolerance. Using the screening algorithm for type 2 diabetes as advocated by the American Diabetes Association, 68% of patients with impaired glucose tolerance and 66% of patients with type 2 diabetes would have been missed. No abnormalities in the MC4R and BDNF genes were detected.

Conclusions: Impaired glucose tolerance and type 2 diabetes are far more common in obese European children of Caucasian origin than previously thought. Using fasting glucose levels as the main screening tool appears to be insufficient in detecting these children.

These papers are among the first to report on large studies for the prevalence or risk factors for type 2 diabetes or the metabolic syndrome in European children. The paper by Weiss et al.[14], based on a multiethnic population of obese adolescents, shows that the prevalence of the metabolic syndrome could be as high as 50%; moreover, even in this population of obese or extremely obese children, worsening of obesity drastically affects metabolic complications. The study by Viner et al. performed on 103 obese children in the UK emphasizes on an important observation: even in this at-risk population disorders of glucose tolerance are not frequent ($<12\%$) contrasting with a high frequency of insulin resistance (30%) even in the prepubertal group. The paper by Reinehr et al. underlines that type 2 diabetes can be silent in children. However, it is always associated with obesity, the metabolic syndrome and often with acanthosis nigricans. These observations indicate in which obese children, disorders of glucose tolerance should be searched for. The last two papers monitor the frequency of disorders of glucose tolerance in large samples of obese Caucasian children. Overt type 2 diabetes is

rare (<5%) and impaired glucose tolerance is observed in 2.1% of the children in the paper by Wabitsch et al., whereas it is found in 30% of a highly selected subgroup of children in the paper by Wiegand et al. The data also show that in Europe, Caucasian children and not only those from ethnic minorities can be affected.

These results call for several remarks:

- The prevalence of type 2 diabetes in children and adolescents in Europe is low even in high- or very-high-risk groups (in the paper by Wiegand et al. for instance) both in absolute numbers and in comparison to what is observed in the USA [14].
- Clearly, the metabolic complications of obesity are not as frequent in Europe as in the USA. Whether it is a 'true' difference or whether this is linked to the lesser extent and degree of obesity in Europe remains to be determined. In the latter case, this indicates that type 2 diabetes in children will reach 'epidemic' levels within 20 or 30 years.
- Ethnicity does not appear to be a strong risk factor for these complications in Europe.
- Risk factors may vary across populations or continents but the degree of obesity and a family history of type 2 diabetes remain strong predictors in any population. Performing studies in different groups allows to document the high-risk groups in whom screening for the metabolic complications should be performed in clinical practice.

References

1. Dulloo AG, Girardier L: Adaptive role of energy expenditure in modulating body fat and protein deposition during catch-up growth after early undernutrition. *Am J Clin Nutr* 1993;58:614–621.
2. Dulloo AG: Human pattern of food intake and fuel-partitioning during weight recovery after starvation: a theory of autoregulation of body composition. *Proc Nutr Soc* 1997;56:25–40.
3. Dulloo AG, Jacquet J, Montani JP: Pathways from weight fluctuations to metabolic diseases: focus on maladaptive thermogenesis during catch-up fat. *Int J Obes Relat Metab Disord* 2002;26(suppl 2):S46–S57.
4. Crescenzo R, Samec S, Antic V, Rohner-Jeanrenaud F, Seydoux J, Montani JP, Dulloo AG: A role for suppressed thermogenesis favoring catch-up fat in the pathophysiology of catch-up growth. *Diabetes* 2003;52:1090–1097.
5. Dunger DB, Ong KKL, Huxtable SJ, Sherif A, Woods KA, Ahmed ML, Golding J, Pembrey ME, Ring S, et al, the ALSPAC Study Team: Association of the INS-VNTR with size at birth. *Nat Genet* 1998;19:98–100.
6. Lindsay RS, Hanson RL, Wiedrich C, Knowler WC, Bennett PH, Baier LJ: The insulin gene variable number tandem repeat class I/III polymorphism is in linkage disequilibrium with birth weight but not type 2 diabetes in the Pima population. *Diabetes* 2003;52:187–193.
7. Bennett AJ, Sovio U, Ruokonen A, Martikainen H, Pouta A, Taponen S, Hartikainen AL, King VJ, Elliott P, Jarvelin MR, et al: Variation at the insulin gene VNTR (variable number tandem repeat) polymorphism and early growth: studies in a large Finnish birth cohort. *Diabetes* 2004;53:2126–2131.
8. Bennett A, Sovio U, Ruokonen A, Martikainen H, Pouta A, Taponen S, Hartikainen A, Franks S, Peltonen L, Elliott P, et al: No association between insulin gene variation and adult metabolic phenotypes in a large Finnish birth cohort. *Diabetologia* 2005;48:886–891.
9. Vu-Hong Ta, Durand E, Deghmoun S, Boutin P, Chevenne D, Czernichow P, Froguel P, Levy-Marchal C: The insulin gene VNTR does not contribute to low birth weight but associates with insulin resistance in young adults born small for gestational age (abstract). ESPE/LWPES Meeting, 2005.
10. Moran A, Sinaiko AR: Influence of intrauterine environment on development of insulin resistance. *J Pediatr* 2000;136:567–569.
11. Sinaiko AR, Steinberger J, Moran A, Prineas RJ, Jacobs DR: Relation of insulin resistance to blood pressure in childhood. *J Hypertens* 2002;20:509–517.
12. Sinaiko A, Jacobs D, Steinberger J, Moran A, Luepker R, Rocchini A, Prineas R: Insulin resistance syndrome in childhood: associations of the euglycemic insulin clamp and fasting insulin with fatness and other risk factors. *J Pediatr* 2001;139:700–707.
13. Moran A, Jacobs DR, Steinberger J, Hong CP, Prineas R, Luepker R, Sinaiko AR: Insulin resistance during puberty: results from clamp studies in 357 children. *Diabetes* 1999;48:2039–2044.
14. Weiss R, Dufour S, Taksali SE, Tamborlane WV, Petersen KF, Bonadonna RC, Boselli L, Barbetta G, Allen K, Rife F, et al: Prediabetes in obese youth: a syndrome of impaired glucose tolerance, severe insulin resistance, and altered myocellular and abdominal fat partitioning. *Lancet* 2003;362:951–957.