Insulin Resistance, the Metabolic Syndrome and Type 2 Diabetes

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This year, a number of physiological breakthroughs have been published and will likely open avenues to the development of new antidiabetic drugs targeting previously unknown targets or unsuspected pathways. If we were in a Chinese calendar this year would be the year of the liver! Many decades after Claude Bernard, the liver is revived as the key organ not only in the regulation of glucose metabolism but more interestingly at the interplay between lipids and glucose metabolism. Several mechanisms are now unmasked at the molecular level.

From a clinical point of view, a number of papers, either based on representative study populations or using modern investigations, draw our attention to the fact that a rapidly growing number of children demonstrate a profile of elevated cardiovascular risks whereas the mean BMI increases worldwide in teenagers and adolescents. However, no major trial or major intervention study has been reported in this population aiming at reducing the burden of the renowned cardiovascular risks in the future.

Mechanisms of the year

Beta-cell ABCA1 influences insulin secretion, glucose homeostasis and response to thiazolidinedione treatment

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Introduction: Type 2 diabetes is characterized by both peripheral insulin resistance and reduced insulin secretion. The reasons for β -cell dysfunction in this disease are not completely understood but may include the accumulation of toxic lipids within this cell type.

Results: The role of Abca1, a cellular cholesterol transporter, was tested for cholesterol homeostasis and insulin secretion in β -cells. Mice with specific inactivation of Abca1 in β -cells had markedly impaired glucose tolerance and defective insulin secretion but normal insulin sensitivity. Islets isolated from these mice showed altered cholesterol homeostasis and impaired insulin secretion in vitro. Rosiglitazone, an activator of the peroxisome proliferator-activated receptor- γ , which upregulates Abca1 in β -cells, requires β -cell Abca1 for its beneficial effects on glucose tolerance.

Conclusion: These experiments establish a new role for Abca1 in β -cell cholesterol homeostasis and insulin secretion, and suggest that cholesterol accumulation may contribute to β -cell dysfunction in type 2 diabetes.

Although the paper is not an easy one to read, this is a real breakthrough of the year and identifies a novel mechanism. A transporter molecule involved in the intracellular metabolism of cholesterol modulates insulin secretion. It does so by altering the trafficking of insulin towards exocytosis granules and does not affect the synthesis of the molecule. These findings have direct therapeutic implications. Rosiglitazone, used as oral antidiabetic agent, is known as an insulin sensitizer. Here it is shown that it can improve insulin secretion by the β -cells. The gene of the cholesterol transporter is upregulated by PPAR- γ , which itself is activated by the thiazolidinediones. This very process contributes to the beneficial effect of thiazolidinediones in the treatment of type 2 diabetes, which is still not fully understood.

Induction of leptin resistance through direct interaction of C-reactive protein with leptin

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Nat Med 2006;12:425–432

Introduction: The mechanisms underlying leptin resistance are still being defined. Several serum leptin-interacting proteins have been isolated from human sera by leptin-affinity chromatography and identified by mass spectrometry and immunochemical analysis.

Results: One of the major proteins identified by chromatography is C-reactive protein (CRP). In vitro, human CRP directly inhibits the binding of leptin to its receptors and blocks its ability to signal in cultured cells. In vivo, infusion of human CRP into ob/ob mice blocked the effects of leptin upon satiety and weight reduction. In mice that express a transgene encoding human CRP, the actions of human leptin were completely blunted. Physiological concentrations of leptin can stimulate expression of CRP in human primary hepatocytes. Recently, human CRP has been correlated with increased adiposity and plasma leptin.

Conclusion: The results suggest a potential mechanism contributing to leptin resistance, by which circulating CRP binds to leptin and attenuates its physiological functions.

The concept of leptin resistance was suggested some years ago but the potential molecular mechanisms of this resistance have not yet been elucidated. For example, elevation of the protein suppressor of cytokine signaling-3 (SOCS-3) [1], which is induced by leptin, was proposed as a negative regulator of proximal leptin signaling blunting the action of leptin in the central nervous system. The authors suggested a new pathway involving CRP. Five serum leptin-interacting proteins were detected and one was identified as CRP. CRP seemed to bind directly to leptin, and thus inhibited the ability of leptin to activate STAT3 and PI_3K . Furthermore, administration of human CRP attenuated the effects of human leptin on food intake, body weight, blood glucose and lipid metabolism in the ob/ob mice. They suggested an adipo-hepato-regulatory loop that involves stimulation of CRP expression by leptin and the feedback inhibition of leptin action in the central nervous system and in the periphery by CRP. Their findings point to a potential contribution of CRP to the pathogenesis of obesity and its metabolic complications, reinforcing the link between obesity and inflammation. Disruption of leptin-CRP interaction may thus become a new therapeutic objective for the treatment of obesity.

New mechanisms

LXR: one transcription factor fits all

The liver X receptor (LXR) and hepatic lipogenesis. The carbohydrate-response element-binding protein is a target gene of LXR

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Introduction: The liver X receptors, LXR- α (NR1H3) and LXR- β (NR1H2), are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily. LXRs play a critical role in cholesterol homeostasis and bile acid metabolism. In addition, oral administration of LXR agonists to mice results in elevated hepatic fatty acid synthesis and steatosis and increased secretion of triglyceride-rich very low density lipoprotein resulting in hypertriglyceridemia. This increased hepatic lipogenesis has been largely attributed to the LXR-dependent upregulation of sterol regulatory element-binding protein 1c (SREBP-1c) expression. However, it has been reported that treating Srebp-1c null mice with the synthetic LXR agonist T0901317 still results in enhanced expression of many lipogenic genes, suggesting additional mechanisms by which LXR can enhance hepatic lipogenesis.

Results: The carbohydrate response element-binding protein (ChREBP) is an LXR target that independently enhances the upregulation of select lipogenic genes. The ChREBP promoter contains functional LXR-binding sites that confer receptor-dependent binding and transactivation. T0901317 treatment of mice is associated with upregulation of the ChREBP target gene, liver-type pyruvate kinase. Therefore, activation of LXR not only increases ChREBP mRNA via enhanced transcription but also modulates ChREBP activity.

Conclusion: This establishes LXR as a master lipogenic transcription factor, as it directly regulates both SREBP-1c and ChREBP to enhance hepatic fatty acid synthesis.

The nuclear receptor LXR is a glucose sensor

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Introduction: The liver has a central role in glucose homeostasis, as it has the distinctive ability to produce and consume glucose. On feeding, glucose influx triggers gene expression changes in hepatocytes to suppress endogenous glucose production and convert excess glucose into glycogen or fatty acids to be stored in adipose tissue. This process is controlled by insulin, although debate exists as to whether insulin acts directly or indirectly on the liver. In addition to stimulating pancreatic insulin release, glucose also regulates the activity of ChREBP, a transcription factor that modulates lipogenesis.

Results: Another mechanism whereby glucose determines its own fate is reported: glucose binds and stimulates the transcriptional activity of the liver X receptor (LXR), a nuclear receptor that coordinates hepatic lipid metabolism. D-Glucose and D-glucose-6-phosphate are direct agonists of both LXR- α and LXR- β . Glucose activates LXR at physiological concentrations expected in the liver and induces expression of LXR target genes with efficacy similar to that of oxysterols, the known LXR ligands. Cholesterol homeostasis genes that require LXR for expression are upregulated in liver and intestine of fasted mice re-fed with a glucose diet, indicating that glucose is an endogenous LXR ligand.

Conclusion: LXR is a transcriptional switch that integrates hepatic glucose metabolism and fatty acid synthesis.

For a long time, type 2 diabetes has been regarded exclusively as a disorder of glucose metabolism. It is only recently that lipid metabolism has been shown to interfere with insulin sensitivity, at both levels of the muscle and the liver [2, 3], and also with insulin secretion. LXR, a hepatic transcription factor, was known to be a lipid sensor acting as a messenger between oxysterols, dietary-derived nutrients, and key enzymes of cholesterol metabolism [4]. The molecular mechanism has been identified with the direct and specific activation of another transcription factor, SREBP-1c. Now it is shown that LXR is also able to directly activate both expression and activity of ChREBP, a major player in the regulation of glucose homeostasis in the liver [4, 5]. Altogether the majority of the ChREBP target genes are regulated, directly or indirectly, by LXR itself (pyruvate-kinase, fatty acid synthase, acetyl-CoA carboxylase ...), LXR-activated genes via SREBP-1c and ChREBP will promote fatty acids synthesis from products derived from glycolysis. Then, LXR serves as a major transcriptional regulator, which integrates glucose

conversion and lipids production in the liver. It is also demonstrated that LXR may act as a glucose sensor responding to increased glucose uptake by the liver. Among others, this integrated loop can explain why a low-fat, high-carbohydrate diet can induce hypertriglyceridemia. More fascinating are the routes open by such a hepatic cross-talk for the development of novel drugs.

Inhibition of protein kinase-C ϵ prevents hepatic insulin resistance in non-alcoholic fatty liver disease

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Introduction: Non-alcoholic fatty liver disease is strongly associated with hepatic insulin resistance and type 2 diabetes mellitus, but the molecular signals linking hepatic fat accumulation to hepatic insulin resistance are unknown.

Results: Three days of high-fat feeding in rat results specifically in hepatic steatosis and hepatic insulin resistance. In this setting, protein kinase-C ϵ (PKC ϵ), but not other isoforms of PKC, is activated. To determine whether PKC ϵ plays a causal role in the pathogenesis of hepatic insulin resistance, we treated rats with an antisense oligonucleotide against PKC ϵ and subjected them to 3 days of high-fat feeding. Knocking down PKC ϵ expression protects rats from fat-induced hepatic insulin resistance and reverses fat-induced defects in hepatic insulin signaling. Furthermore, we show that PKC ϵ associates with the insulin receptor in vivo and impairs insulin receptor kinase activity both in vivo and in vitro.

Conclusion: These data support the hypothesis that PKC ϵ plays a critical role in mediating fat-induced hepatic insulin resistance and represents a novel therapeutic target for type 2 diabetes.

For many years the work published by Shulman et al. [6–8] has both comforted and revisited the old concept proposed by Randle et al. [3]: the glucose-fatty acids competition on insulin sensitivity. Elevated circulating fatty acids contribute to insulin resistance. Shulman was the first to describe the competition first with glucose transport and then with insulin signaling in the muscle. Here, using the elegant technique of antisense oligonucleotides in vivo, able to specifically knock down the activity of PKC ϵ , the same authors can demonstrate that PKC ϵ is the molecule that interferes in the liver with the tyrosine phosphorylation of IRS-2 and the insulin receptor upon the activation of metabolites derived from fatty acids. This is an additional example where the precise identification of the crucial step of a physiological process will help develop pharmaceutical agents. In this example, blocking PKC ϵ may hamper the development of insulin resistance in obesity.

Bile

Prevention and treatment of obesity, insulin resistance, and diabetes by bile acid-binding resin

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Diabetes 2007;56:239–247

Introduction: Bile acid-binding resins, such as cholestyramine and colestimide, have been clinically used as cholesterol-lowering agents. These agents bind bile acids in the intestine and reduce enterohepatic circulation of bile acids, leading to accelerated conversion of cholesterol to bile acids. A significant improvement in glycemic control was reported in patients with type 2 diabetes whose hyperlipidemia was treated with bile acid-binding resins. To confirm the effect of such drugs on glucose metabolism and to investigate the underlying mechanisms, an animal model of type 2 diabetes was given a high-fat diet with and without colestimide.

Results: Diet-induced obesity and fatty liver were markedly ameliorated by colestimide without decreasing the food intake. Hyperglycemia, insulin resistance, and insulin response to glucose, as well as dyslipidemia,

were markedly and significantly ameliorated by the treatment. Gene expression in the liver indicated reduced expression of a small heterodimer partner, a pleiotropic regulator of diverse metabolic pathways, as well as of genes for both fatty acid synthesis and gluconeogenesis, by treatment with colestimide.

Conclusion: This study provides a molecular basis for a link between bile acids and glucose metabolism and suggests the bile acid metabolism pathway as a novel therapeutic target for the treatment of obesity, insulin resistance, and type 2 diabetes.

As seen above, the liver is a central organ for the regulation of the metabolism of both glucose and lipids. Consequently, hepatic cholesterol metabolism is important in the pathogenesis and dyslipidemia and hyperglycemia. It is well known that anion exchange resins bind bile acids in the intestine and promote accelerated conversion to bile acids. It is shown here in an animal model *in vivo* that the chronic administration of acid-binding resins improved markedly hyperglycemia and dyslipidemia induced by a high-fat diet in mice. This was not due to decreased food intake, but to the modification of the expression of the hepatic enzymes implicated in cholesterol metabolism and in fatty acids and glucose metabolism. A small heterodimer partner was the central regulatory element interfering with the different metabolic pathways. Once more with this example, it is emphasized on the critical importance of the liver in the regulation of glucose and lipids metabolism and on the importance of the cross-talk between these pathways. The important caveat with bile acid resins is that they induce toxic side effects in the liver limiting so far their use in clinical practice. However, a large and promising field of reflection is open.

New hormones

Deficiency of interleukin-18 in mice leads to hyperphagia, obesity and insulin resistance

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Nat Med 2006;12:650–656

Introduction: Because the level of interleukin-18 (IL-18) was found to be increased in individuals with type 2 diabetes mellitus, obesity and polycystic ovary syndrome, it has been hypothesized that increased of IL-18 level may play a role in insulin resistance.

Results: Hyperphagia, obesity and insulin resistance are observed in knockout mice deficient in IL-18 or IL-18 receptor, and in mice transgenic for expression of IL-18-binding protein. Obesity of IL18^{-/-} mice resulted from accumulation of fat tissue based on increased food intake. IL18^{-/-} mice also had hyperinsulinemia, consistent with insulin resistance and hyperglycemia. Insulin resistance was secondary to obesity induced by increased food intake and occurred at the liver level as well as at the muscle and fat-tissue level. The molecular mechanisms responsible for the hepatic insulin resistance in the IL18^{-/-} mice involved an enhanced expression of genes associated with gluconeogenesis in the liver of IL18^{-/-} mice, resulting from defective phosphorylation of STAT3. Recombinant IL-18 (rIL-18) administered intracerebrally inhibited food intake. In addition, rIL-18 reversed hyperglycemia in IL18^{-/-} mice through activation of STAT3 phosphorylation.

Conclusion: These findings indicate a new role of IL-18 in the homeostasis of energy intake and insulin sensitivity.

IL-18 is a novel cytokine, member of the IL-1 family of proteins. Many of the actions of IL-18 are mediated by interferon (IFN)- γ , but several effects (for example, induction of joint inflammation and septic shock) are independent of the latter cytokine. Because the level of IL-18 was found to be increased in individuals with type 2 diabetes mellitus, obesity and polycystic ovary syndrome, it has been hypothesized that increased of IL-18 level may play a role in insulin resistance [9, 10].

The paper shows that there is a marked increase in body weight in IL-18-knockout (IL18^{-/-}) and IL-18 receptor-knockout (IL18r1^{-/-}) mice compared to wild-type littermates. The increased body weight of these mice is associated with enlarged fat mass resulting from enhanced food intake. The metabolic rate did not seem to be affected by the absence of IL-18 and the hypothalamus was considered as the primary target organ of IL-18. The data also show that IL-18-knockout (IL18^{-/-}) and IL-18 receptor-knockout (IL18r1^{-/-}) mice are insulin resistant and hyperglycemic supporting the role of IL-18 in glucose homeostasis but suggesting that these effects are indirect, through increased food intake and weight gain. In addition, administration of IL-18 recombinant improves glucose tolerance and insulin sensitivity. Finally the effects of exogenous IL-18 on glucose metabolism are mediated by activation of STAT3 phosphorylation.

The authors are the first to involve IL-18 in energy balance (intake vs. expenditure) and to suggest that in individuals with type 2 diabetes mellitus increased IL-18 levels may indicate an attempt of the organism to counteract hyperglycemia. Alternatively, a state of IL-18 resistance, similar to insulin and leptin resistance, could be envisioned in individuals with type 2 diabetes.

Oncogenic steroid receptor coactivator-3 is a key regulator of the white adipogenic program

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Introduction: The white adipocyte is at the center of dysfunctional regulatory pathways in various pathophysiological processes, including obesity, diabetes, inflammation, and cancer.

Results: The oncogenic steroid receptor coactivator-3 (SRC-3) is a critical regulator of white adipocyte development. Indeed, in SRC-3^{-/-} mouse embryonic fibroblasts, adipocyte differentiation was severely impaired, and re-expression of SRC-3 was able to restore it. The early stages of adipocyte differentiation are accompanied by an increase in nuclear levels of SRC-3, which accumulates to high levels specifically in the nucleus of differentiated fat cells. Moreover, SRC-3^{-/-} animals showed reduced body weight and adipose tissue mass with a significant decrease of the expression of peroxisome proliferator-activated receptor- γ_2 (PPAR- γ_2), a master gene required for adipogenesis. At the molecular level, SRC-3 acts synergistically with the transcription factor CAAT/enhancer-binding protein to control the gene expression of PPAR- γ_2 .

Conclusion: These data suggest a crucial role for SRC-3 as an integrator of the complex transcriptional network controlling adipogenesis.

Actually this is not a hormone, but a coactivator of nuclear receptors and in that way may interact with the effects of different hormones. Several nuclear factors are known to regulate adipogenesis, such as PPAR- γ , in the rather late steps. Several coregulators have been identified that mediate the functions of nuclear receptors and are therefore likely to control different steps of the development of adipose tissue. Interestingly, most of these coactivators of PPAR- γ look specific for a given physiological target. SRC-3 is one such coactivator that has been described as an oncogene or as a tumor suppressor depending on the cellular context. When the activity of this coactivator is suppressed in the knockout model the animals present with a lean phenotype and it is shown that adipogenesis is severely impaired in the absence of SRC-3. Indeed, SRC-3 acts as a coregulator of PPAR- γ and controls its expression in adipocytes. This coactivator can modulate the late steps of adipocyte differentiation. From a biochemical point of view it is easier to block the action of a coactivator than to specifically block one of the multiple effects of the activation of a transcription factor such as PPAR- γ . In this respect, the data presented here open opportunities to develop molecules able to interfere with adipogenesis.

Diabetes mellitus screening in pediatric primary care

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Objective: The goal was to determine the rates of diabetes screening and the prevalence of screening abnormalities in overweight and non-overweight individuals in an urban primary care clinic. This study was a retrospective chart review conducted in a hospital-based urban primary care setting. Data for patients who were 10–19 years of age and had ≥ 1 BMI measurement between September 1, 2002, and September 1, 2004, were extracted from the hospital electronic health record.

Results: A total of 7,710 patients met the study criteria. Patients were 73.0% black or Hispanic and 47.0% female; 42.0% of the children exceeded normal weight, with 18.2% at risk for overweight and 23.8% overweight. On the basis of BMI, family history, and race, 8.7% of patients met American Diabetes Association (ADA) criteria for type 2 diabetes mellitus screening, and 2,452 screening tests were performed for 1,642 patients. Female gender, older age group, and family history of diabetes were associated with screening. Increasing the BMI percentile was associated with screening, exhibiting a dose-response relationship. Screening rates were significantly higher (45.4 vs. 19.0%) for patients who met the ADA criteria; however, less than one half of adolescents who should have been screened were screened. Abnormal glucose metabolism was seen for 9.2% of patients screened.

Conclusions: This study shows that, although pediatricians are screening for diabetes mellitus, screening is not being conducted according to the ADA consensus statement. Point-of-care delivery of consensus recommendations could increase provider awareness of current recommendations, possibly improving rates of systematic screening and subsequent identification of children with laboratory evidence of abnormal glucose metabolism.

The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study

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Pediatrics 2006;118:1510–1518

Objective: The goal was to estimate the prevalence of diabetes mellitus in youths <20 years of age in 2001 in the USA, according to age, gender, race/ethnicity, and diabetes type.

Methods: The SEARCH for Diabetes in Youth Study is a six-center observational study conducting population-based ascertainment of physician-diagnosed diabetes in youths. Census-based denominators for four geographically-based centers and enrollment data for two health plan-based centers were used to calculate prevalence. Age-, gender-, and racial/ethnic group-specific prevalence rates were multiplied by US population counts to estimate the total number of US youths with diabetes.

Results: 6,379 US youths with diabetes in 2001 were identified among a population of approximately 3.5 million. Crude prevalence was estimated as 1.8 cases per 1,000 youths, being much lower for youths 0–9 years of age (0.8/1,000 youths) than for those 10–19 years of age (2.8/1,000 youths). Non-Hispanic white youths had the highest prevalence (1.1/1,000 youths) in the younger group. Among 10- to 19-year-old youths, black youths (3.2/1,000 youths) and non-Hispanic white youths (3.2/1,000 youths) had the highest rates, followed by American Indian (2.28/1,000 youths), Hispanic youths (2.2/1,000 youths), and Asian/Pacific Islander youths (1.34/1,000 youths). Among younger children, type 1 diabetes accounted for $\geq 80\%$ of diabetes; among older youths, the proportion of type 2 diabetes ranged from 6% (0.2/1,000 youths for non-Hispanic white youths) to 76% (1.7/1,000 youths for American Indian youths). It is estimated that 154,369 youths had physician-diagnosed diabetes in 2001 in the USA.

Conclusions: The overall prevalence estimate for diabetes in children and adolescents was approximately 0.18%. Type 2 diabetes was found in all racial/ethnic groups but was generally less common than type 1, except in American Indian youths.

These two articles clearly show the increasing prevalence of diabetes in children and the difficulties encountered to adequately screen for the disease. The SEARCH for Diabetes in Youth Study is one of the largest surveillance surveys on diabetes in youths conducted in the USA to date [11]. Several reports have raised concerns about diabetes and particularly type 2 diabetes in minority populations. However, it is the first population-based prevalence estimates in two subgroups of children and adolescents: Hispanic and Asian/Pacific Islander (22 and 33% of cases of diabetes in youths 10–19 years of age respectively), based on validated cases of type 2 diabetes. SEARCH provides the most comprehensive data to date on the overall burden of diabetes among youths. By extrapolation, they estimate that 154,000 of 80.7 million children and adolescents throughout the USA had physician-diagnosed diabetes in 2001 (1 of every 523 youths).

Anand et al. [12] offered a view of the current screening practices for diabetes in an urban pediatric primary care center as it was recommended in 2000 by the ADA. Two problems emerged: first only less than half of children who met ADA criteria were screened, and secondly, 3 out of 4 patients screened had tests different from those recommended by the ADA. This emphasizes the fact that more education is needed on consensus recommendations, screening strategies and interpretation of results.

Cardiovascular risk profile in childhood

Lipid abnormalities are prevalent in youth with type 1 and type 2 diabetes: the SEARCH for Diabetes in Youth Study

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Objective: Assessment of the prevalence of serum lipid abnormalities in US youths with type 1 or type 2 diabetes. The SEARCH for Diabetes in Youth Study was a cross-sectional, population-based study, conducted in six centers. Subjects were 2,448 youths with diabetes who had a study examination. Outcome measures were fasting measures of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides.

Results: The overall prevalence of high total cholesterol concentration (>240 mg/dl) was 5%; the overall prevalence of high LDL-C (>160 mg/dl) was 3%, and the overall prevalence of high triglyceride (>400 mg/dl) was 2%. About half of the participants (48%) had an LDL-C concentration above the optimal level of 100 mg/dl. Among youths aged ≥ 10 years, the prevalence of abnormal lipids was higher in type 2 ($n = 283$) than in type 1 diabetes ($n = 1963$): 3% vs. 19% had total cholesterol concentration >200 mg/dl; 24 vs. 15% had LDL-C concentration >130 mg/dl; 29 vs. 10% had triglyceride concentration >150 mg/dl, and 44 vs. 12% had HDL-C concentration <40 mg/dl. Only 1% of the youths were receiving pharmacologic therapy for dyslipidemia.

Conclusions: A substantial proportion of young patients with diabetes have abnormal serum lipids.

Prevalence of cardiovascular disease risk factors in US children and adolescents with diabetes: the SEARCH for Diabetes in Youth Study

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Diabetes Care 2006;29:1891–1896

Objective: The purpose of this study was to determine the prevalence and correlates of selected cardiovascular disease risk factors among youths aged <20 years with diabetes. The analysis included 1,083 girls and 1,013 boys examined as part of the SEARCH for Diabetes in Youth Study, a multicenter, population-based study of youths 0–19 years of age with diabetes. Diabetes type was determined by a biochemical algorithm based on diabetes antibodies and fasting C-peptide level. Cardiovascular risk factors were defined as follows: HDL cholesterol <40 mg/dl; age- and sex-specific waist circumference >90th percentile; systolic or diastolic blood pressure >90th percentile for age, sex, and height or taking medication for high blood pressure, and triglycerides >110 mg/dl.

Results: The prevalence of having at least two cardiovascular risk factors was 21%. The prevalence was 7% among children aged 3–9 years and 25% in youths aged 10–19 years ($p < 0.0001$), 23% among girls and 19% in boys ($p = 0.04$), 68% in American Indians, 37% in Asian/Pacific Islanders, 32% in African-Americans, 35% in Hispanics, and 16% in non-Hispanic whites ($p < 0.0001$). At least two cardiovascular risk factors were present in 92% of youths with type 2 and 14% of those with type 1A diabetes ($p < 0.0001$). In multivariate analyses, age, race/ethnicity, and diabetes type were independently associated with the odds of having at least two cardiovascular risk factors ($p < 0.0001$).

Conclusions: Many youths with diabetes have multiple cardiovascular risk factors. Recommendations for weight, lipid, and blood pressure control in youths with diabetes need to be followed to prevent or delay the development of cardiovascular as these youngsters mature.

Intima media thickness in childhood obesity: relations to inflammatory marker, glucose metabolism and blood pressure

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Metabolism 2006;55:113–118

Introduction: Obesity in childhood is discussed to be associated with hypertension, dyslipidemia, impaired glucose metabolism, and chronic inflammation. It has not yet been studied in obese children which of these cardiovascular risk factors are related to intima media thickness (IMT), a non-invasive marker for early atherosclerotic changes.

Results: Clinical data (age, sex, pubertal stage, percentage of body fat, SD score of body mass index (SDS-BMI)) and measured systolic blood pressure and diastolic blood pressure, triglycerides, high- and low-density lipoprotein cholesterol, glucose, insulin, and high-sensitivity C-reactive protein (CRP) were collected in 96 obese children (median age 11 years). The control group was composed of 25 non-obese children of the same age, sex, and pubertal stage. The carotid IMT of all the patients was measured by B-mode ultrasound with a 14-MHz linear transducer. Obese children demonstrated a significantly ($p < 0.001$) thicker intima media (median 0.6 mm) as compared with the control group (median thickness 0.4 mm). IMT was significantly correlated to the SDS-BMI ($r = 0.38$, $p < 0.001$), percentage of body fat ($r = 0.39$, $p < 0.001$), systolic blood pressure ($r = 0.39$, $p < 0.001$) and diastolic blood pressure ($r = 0.29$, $p = 0.002$), glucose ($r = 0.30$, $p = 0.001$), and high-sensitivity CRP levels ($r = 0.29$, $p = 0.002$). In stepwise backward multiple linear regression analysis, IMT correlated significantly to BMI ($r^2 = 0.05$, $p = 0.044$), systolic blood pressure ($r^2 = 0.15$, $p = 0.013$), glucose ($r^2 = 0.05$, $p = 0.028$), and high-sensitivity CRP ($r^2 = 0.07$, $p = 0.005$). Because IMT is increased in obese children, vascular changes in obesity seem to occur already in childhood.

Conclusion: These changes are related to the cardiovascular risk factors of obesity, especially hypertension, chronic inflammation, and impaired glucose metabolism.

One could say that these papers are nothing new and this is true to some extent! We all know that diabetes and obesity are diseases with an elevated risk for cardiovascular morbidity and mortality. We all know that, in this respect, blood pressure and lipid profiles should be monitored carefully in the patients. What is more novel is the study population in the first two papers. The SEARCH program [11] is an outstanding population study aimed at (1) measuring the prevalence and the incidence of diabetes in youths, (2) refining the characteristics and the definition of the different types of diabetes in this population, and (3) evaluating comorbidities. Because the data is population-based and not from specialized clinics, the weight of the observation is much higher. The last paper shows that a risk profile can be detected in children and, more importantly, that obesity affects the major surrogate measurement of vascular disease: the thickness of the carotid wall is already increased as early as 11 years of age in obese children. These studies demonstrate that a fair proportion of diabetic children have increased blood pressure and profound changes in lipids profiles. This is true of patients with type 1 diabetes, even before the age of 10 years: 19% of diabetic children had a total cholesterol level >200 mg/dl (5.2 mmol/l), 9% had triglycerides >200 mg/dl (2.2 mmol/l), and 48% had LDL cholesterol >140 mg/dl (3.6 mmol/l).

What is outrageous (at least to me – C.L.-M.) is that no large-scale trial has been implemented in this population to test the feasibility and the efficacy of drugs largely prescribed in adults. This shortcoming is even reflected by the lack of interest of the pharmaceutical laboratories for the pediatric patient population.

Concepts revised

Testing the accelerator hypothesis: body size, β -cell function, and age at onset of type 1 (autoimmune) diabetes

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Objective: The 'accelerator hypothesis' predicts that fatness is associated with an earlier age at onset of type 1 diabetes. This hypothesis was tested using data from the SEARCH for Diabetes in Youth Study.

Results: Subjects were 449 youths aged <20 years at diagnosis who had positive results for diabetes antibodies measured 3–12 months after diagnosis (mean 7.6 months). The relationships between age at diagnosis and fatness were examined using BMI as measured at the SEARCH visit and reported birth weight, both expressed as SD scores (SDSs). In the univariate analysis, BMI-SDS was not related to age at diagnosis. In multiple linear regression, adjusted for potential confounders, a significant interaction was found between BMI-SDS and fasting C-peptide on onset age ($p < 0.0001$). This interaction remained unchanged after additionally controlling for number and titers of diabetes antibodies. An inverse association between BMI and age at diagnosis was present only among subjects with FCP levels below the median (<0.5 ng/ml) (regression coefficient -7.9 , $p = 0.003$). A decrease of 1 SDS in birth weight (639 g) was also associated with an approximately 5-month earlier age at diagnosis ($p = 0.008$), independent of sex, race/ethnicity, current BMI, fasting C-peptide, and number of diabetes antibodies.

Conclusions: Increasing BMI is associated with younger age at diagnosis of type 1 diabetes only among those US youths with reduced β -cell function. The intrauterine environment may also be an important determinant of age at onset of type 1 diabetes.

The 'accelerator hypothesis' proposes that the decrease in age at onset of type 1 diabetes is due to the increased body size and fatness of children [13]. The mechanism could be either through an excessive demand on the β -cells to face the insulin resistance due to fatness or the aggravation of the preexisting autoimmune process with increased insulin release and consequently increased presentation of the autoantigen.

Data have been conflicting in the literature to ascertain this hypothesis [14–17]. Here, based on the SEARCH network, an inverse relationship between BMI and age at onset of diabetes was seen only in

children with low C-peptide secretion. These data suggest that the 'acceleration' toward diabetes, if any, occurs only at a very late phase of the autoimmune disease just at the time of the clinical manifestation, when the function of the β -cells is already largely compromised.

Clinical practice Obesity

A study of central fatness using waist-to-height ratios in UK children and adolescents over two decades supports the simple message – 'keep your waist circumference to less than half your height'

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Introduction: To examine the influence of age and gender on the waist:height ratio (WHtR) in children and to compare changes over time in WHtR, a measure of central fatness in British children. Representative cross-sectional surveys in 1977, 1987 and 1997.

Results: Survey 1: children aged 5–16 years measured in 1977 (boys) and 1987 (girls) ($n = 8,135$) and Survey 2: children aged 11–16 measured in 1997 ($n = 773$): From Survey 1, WHtR related to age and sex and the proportion of children with a WHtR >0.500 (a boundary value suggested for adults). From Survey 2, comparison of WHtR in children with that from Survey 1 and the actual proportion of children with a WHtR >0.500 compared with the expected proportion using the survey 1 as reference. WHtR decreased with age ($p < 0.01$ for trend), with the mean WHtR being significantly lower in girls ($p < 0.01$). WHtR was significantly greater in children in Survey 2 compared with those measured 10 and 20 years earlier in Survey 1 ($p < 0.0001$). The proportion of children where WHtR exceeded the 0.500 boundary value in Survey 2 was 17% of boys and 11.7% of girls (against 5.0 and 1.5%, respectively, in Survey 1, $p < 0.0001$). The increase in WHtR in boys exceeded that in girls.

Conclusions: Values of WHtR during the past 10–20 years have increased greatly showing that central fatness in children has risen dramatically. WHtR is more closely linked to childhood morbidity than BMI and should be used as an additional or alternative measure to BMI in children as well as adults. A simple public health message that is the same for adults and children of both sexes and all ages could be stated as 'keep your waist circumference to less than half your height'.

In children, as in adults, an upper body or centralized deposition of excess body fat carries an increased risk for obesity-associated metabolic complications. The important observation in this study was the dramatic increase in WHtR in children during the past 10–20 years. This study also demonstrated that WHtR during childhood is influenced by age and by gender and is more closely linked to childhood morbidity than BMI.

The message ('keep your waist circumference less than half your height') is straightforward as well as the concept: when measured in conjunction with height, waist circumference gives an index of proportionality: it's a very easy way to test whether (or not) the amount of upper body fat in relation to height is appropriate. The WHtR is as easy as BMI to calculate and more informative for assessing increased health risk in children relating to an excessive accumulation of central fat.

Promotion of faster weight gain in infants born small for gestational age: is there an adverse effect on later blood pressure?

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Introduction: Being born small for gestational age is associated with later risk factors for cardiovascular disease, such as high blood pressure. Promotion of postnatal growth has been proposed to ameliorate these effects. There is evidence in animals and infants born prematurely, however, that promotion of growth by increased postnatal nutrition increases rather than decreases later cardiovascular risk. The long-term impact of growth promotion in term infants born small for gestational age (birth weight <10th percentile) has already been reported.

Results: Blood pressure was measured at 6–8 years in 153 of 299 (51%) of a cohort of children born small for gestational age and randomly assigned at birth to receive either a standard or a nutrient-enriched formula. The enriched formula contained 28% more protein than standard formula and promoted weight gain. Diastolic and mean (but not systolic) blood pressure was significantly lower in children assigned to standard compared with nutrient-enriched formula (unadjusted mean difference for diastolic blood pressure -3.2 mm Hg; 95% CI -5.8 to -0.5 ; $p = 0.02$) independent of potential confounding factors (adjusted difference -3.5 mm Hg; $p = 0.01$). In observational analyses, faster weight gain in infancy was associated with higher later blood pressure.

Conclusions: In the present randomized study targeted to investigate the effect of early nutrition on long-term cardiovascular health, it was observed that a nutrient-enriched diet increased later blood pressure. These findings support an adverse effect of relative ‘overnutrition’ in infancy on long-term cardiovascular disease risk, have implications for the early origins of cardiovascular disease hypothesis, and do not support the promotion of faster weight gain in infants born small for gestational age.

A lot has been written on the risk of hypertension and type 2 diabetes in individuals born small for gestational age and catch-up growth has been considered as the culprit [18]. However, most of this knowledge comes from observational studies and the beauty of this paper is that it describes an intervention study addressing this important issue. The intervention dealt with early nutrition comparing two groups of SGA infants fed with an enriched formula or not for 9 months. The direct consequence was a faster and larger weight gain in the intervention group, which was not maintained over time. At the age of 6–8 years, although of same body size, the children in the intervention group had higher blood pressure than the control group. In addition, blood pressure correlated with change in weight (z-score) between birth and 9 months of age. Breastfeeding per se had no effect on later blood pressure.

The data clearly suggest that the cost of a faster growth (or weight gain) in infancy is an increase of cardiovascular risks, at least in children born small for gestational age. Although faster weight gain has certainly short-term benefits, the long-term health outcome is more questionable. Don't you think that the important message is that the outcome can be altered by early intervention.

Association of weight gain in infancy and early childhood with metabolic risk in young adults

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Introduction: Early postnatal life has been suggested as an important window during which risks for long-term health may be influenced. The aim of this study was to examine the independent associations between weight gain during infancy (0–6 months) and early childhood (3–6 years) with components of the metabolic syndrome in young adults.

Results: This was a prospective cohort study (The Stockholm Weight Development Study). The study was conducted in a general community. Subjects included 128 (54 males) singletons, followed from birth to 17 years. None of these young adults met the full criteria for the metabolic syndrome. A continuous clustered metabolic risk score was calculated by averaging the standardized values of the following components: waist circumference, blood pressure, fasting triglycerides, high-density lipoprotein cholesterol, glucose, and insulin level. Clustered metabolic risk at age 17 years was predicted by weight gain during infancy (standardized $\beta = 0.16$; $p < 0.0001$) but not during early childhood (standardized $\beta = 0.10$; $p = 0.23$), adjusted for birth weight, gestational age, current height, maternal fat mass, and socioeconomic status at age 17 years. Further adjustment for current fat mass and weight gain during childhood did not alter the significant association between infancy weight gain with the metabolic risk score (standardized $\beta = 0.20$; $p = 0.007$).

Conclusions: Rapid weight gain during infancy (0–6 months) but not during early childhood (3–6 years) predicted clustered metabolic risk at age 17 years. Early interventions to moderate rapid weight gain even at very young ages may help to reduce adult cardiovascular disease risks.

This is the second paper based on the Swedish cohort on the issue of weight gain in childhood and later body composition and metabolic profile [19]. Ken Ong [20, 21] was the first to clearly show that 'crossing centiles' or rapid weight gain in childhood was a strong risk factor for later obesity. The survey can now refine the concept by restricting the critical time-window to the very first months of nutrition (0–6 months) with no further impact of later childhood (3–6 years). Not only overnutrition in this very period may induce permanent and deleterious changes in body composition, but they also induce parallel changes in the metabolic profile. The association of the metabolic 'score' at age 17 and early weight gain was independent of birth weight, gestational age, maternal fat mass and socioeconomic condition. The sweet, chubby baby is nice for his mother but not for its heart!

Consequences of being born small for gestational age

Relationships of maternal and paternal birth weights to features of the metabolic syndrome in adult offspring: an inter-generational study in South India

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Introduction: The association between lower birth weight and metabolic syndrome may result from fetal undernutrition (fetal programming hypothesis) and/or genes causing both low birth weight and insulin resistance (fetal insulin hypothesis). Associations between the birth weight of parents and metabolic syndrome in the offspring were looked for in an Indian cohort.

Results: Men and women (aged 35–68 years), who had been born in Holdsworth Memorial Hospital, Mysore, India, were identified together with the offspring (20–46 years) of these men and women. In total, 283 offspring of 193 mothers and 223 offspring of 144 fathers were studied. Investigations included anthropometry, oral glucose tolerance, plasma insulin and lipid concentrations and blood pressure. The metabolic syndrome was defined using WHO criteria. Among the offspring, lower birth weight was associated with an increased risk of glucose intolerance (impaired glucose tolerance, impaired fasting glucose or type 2 diabetes) and higher cholesterol and triacylglycerol concentrations ($p < 0.05$ for all adjusted for sex and age). Most outcomes in the offspring, including most individual components of the metabolic syndrome, were unrelated to parental birth weight. However, both maternal and paternal birth weight were inversely related to offspring metabolic syndrome (odds ratio 0.36 per kg, $p = 0.053$ for mother-offspring pairs; odds ratio 0.26, $p = 0.04$ for father-offspring pairs, adjusted for offspring age, sex, BMI and socioeconomic status). Maternal birth weight was inversely related to offspring systolic blood pressure ($\beta = -2.5$ mm Hg per kg maternal birth weight; $p = 0.052$).

Conclusions: Factors in both parents may influence the risk of metabolic syndrome in their offspring. There are several possible explanations, but the findings are consistent with the fetal insulin (genetic) hypothesis.

A summary of the findings would be nice. Several models have been proposed to explain the association of restricted fetal growth with later diseases development. The 'thrifty genotype' concept, first proposed by Neel [21], stated that populations have been selected for alleles favoring insulin resistance, which would be advantageous in terms of survival by reducing glucose uptake and limiting body growth at the time of famine but would become detrimental when food supply is abundant. This concept is further developed as 'fetal insulin hypothesis', which proposes that genetically determined insulin resistance results in impaired fetal growth as well as insulin resistance in adult life [22]. As a purely genetic model cannot explain reported effects of human famine during gestation and in experimental animal models, Barker and colleagues [23] proposed the alternative 'thrifty phenotype' model. According to a 'programming' process, they proposed that alteration in fetal nutrition and endocrine status resulted in developmental adaptations that permanently change structure, physiology and metabolism, thereby predisposing individuals to cardiovascular, metabolic and endocrine diseases in adult life [24].

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