Type 2 Diabetes, Metabolic Syndrome, Lipid Metabolism

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The occurrence of type 2 diabetes (T2DM) in youth has been established and numerous reports about prevalence, incidence, and clinical characteristics of these adolescents are continuously documented from all over the world [1]. The highlights of this year's section include: population genetics studies shedding light on both susceptibility to develop T2DM and on novel disease mechanisms; new data on complications of T2DM in youth, and the outcome of a new treatment modality – bariatric surgery in adolescents with T2DM.

Several works have aimed to identify children and adolescents who are at increased risk of developing T2DM. The impact of intrauterine exposure to both maternal obesity and maternal diabetes and the impact of medications such as atypical antipsychotic drugs and valproic acid, on impaired glucose metabolism, the metabolic syndrome and T2DM are reviewed. In parallel the reliability of our diagnostic methods for impaired glucose metabolism in obese children is highlighted as well. In addition, evidence for the efficacy and side effects of various pharmacologic medications in obese children and in adolescents with polycystic ovary syndromes (PCOS) is reviewed. The last section reviews clinical practice recommendations for children with diabetes and dyslipidemia for children with elevated LDL cholesterol and with hypertriglyceridemia.

New mechanism: insights in the pathogenesis of impaired fasting glucose and T2DM

A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk

Bouatia-Naji N, Bonnefond A, Cavalcanti-Proenca C, Sparsø T, Holmkvist J, Marchand M, Delplanque J, Lobbens S, Rocheleau G, Durand E, De Graeve F, Chevre JC, Borch-Johnsen K, Hartikainen AL, Ruokonen A, Tichet J, Marre M, Weill J, Heude B, Tauber M, Lemaire K, Schuit F, Elliott P, Jorgensen T, Charpentier G, Hadjadj S, Cauchi S, Vaxillaire M, Sladek R, Visvikis-Siest S, Balkau B, Levy-Marchal C, Pattou F, Meyre D, Blakemore AI, Jarvelin MR, Walley AJ, Hansen T, Dina C, Pedersen O, Froguel P

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Background: Genetic variation involved in glucose homeostasis may explain susceptibility to insulin resistance and T2DM.

Methods: A genome-wide association for fasting plasma glucose was done in 2,151 nondiabetic French subjects. The contribution of a single nucleotide polymorphism (SNP) to pancreatic β -cell function and diabetes was further studied in 16,094 Europeans.

Results: A SNP, rs1387153, on chromosome 11 was identified as a modulator of fasting plasma glucose. This SNP is located near to MTNR1B which encodes the melatonin receptor. In European populations ($n = 16,094$), the rs1387153 T allele was associated with increased fasting plasma glucose, T2DM and risk of developing hyperglycemia or diabetes over a 9-year period. RT-PCR analyses confirm the presence of MT2 transcripts in neural tissues and show MT2 expression in human pancreatic islets and β cells.

Conclusions: Data suggest a possible link between circadian rhythm regulation and glucose homeostasis through the melatonin signaling pathway.

G-allele of intronic rs10830963 in MTNR1B confers increased risk of impaired fasting glycemia and type 2 diabetes through an impaired glucose-stimulated insulin release: studies involving 19,605 Europeans

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Background: rs10830963, a SNP, is an intronic variant in MTNR1B that showed the strongest signal to fasting plasma glucose using in silico studies.

Methods: Direct genotyping of rs10830963 was done in a large European descent population. The associations of this SNP were studied with isolated impaired fasting glycemia (i-IFG), isolated impaired glucose tolerance (i-IGT), T2DM and measures of insulin release and peripheral and hepatic insulin sensitivity.

Results: The MTNR1B intronic variant, rs10830963, carried most of the effect on FPG and showed the strongest association with FPG and T2D. Further analyses revealed that the rs10830963-G allele increased the risk of i-IFG but not i-IGT. It was associated with a decreased insulin release after oral and intravenous glucose challenges but not after injection of tolbutamide. In elderly twins it was associated to hepatic insulin resistance.

Conclusions: The G-allele of MTNR1B rs10830963 increases risk of T2DM through a state of i-IFG and not through i-IGT. The same allele associates with estimates of β -cell dysfunction and hepatic insulin resistance.

These two fascinating studies lighten the association between melatonin and impaired glucose metabolism.

Melatonin is a neurohormone that regulates the circadian rhythm by translating photoperiodic information from the eyes to the brain. Melatonin functions via two receptors: MT1 and MT2, encoded by MTNR1A and MTNR1B, respectively.

Bouatia-Naji and his colleagues confirmed the expression of MTNR1B in the retina, in the circadian rhythm control center in the brain and in pancreatic tissue, suggesting a role of melatonin in the regulation of insulin secretion. Indeed in healthy individuals, melatonin secretion peaks in the middle of the night, and gradually falls during the day in an opposite manner to insulin levels. Both melatonin secretion and circadian rhythm are impaired in T2DM.

In genome-wide association studies a SNP, rs1387153, was found to be in association with fasting plasma glucose among lean and obese adults and children, and was associated with an increased risk of T2DM. This SNP maps within a 62.1-kb linkage disequilibrium block on chromosome 11 and is located in the 5' region of the gene encoding the melatonin receptor 1B. In the study by Sparsø et al., another SNP, rs10830963, located in the only intron of MTNR1B, was studied as the source of the association signal on fasting plasma glucose and T2DM in more than 11,300 individuals. The G-allele of rs10830963 was associated with increased risk of isolated IFG with the combined IFG and IGT phenotype as well as with overt T2DM but not with isolated IGT, suggesting that this SNP predisposes to T2DM via a state of impaired fasting but not through postprandial glucose levels. Decreased serum insulin levels post-OGTT and post-IVGTT suggest that carriers of the diabetogenic risk allele in MTNR1B may have pancreatic β -cell dysfunction.

Among both adults and children, sleep restriction increases the risk for obesity. Moreover, among adults, sleep duration significantly correlates with the metabolic syndrome and is an independent risk factor for T2DM [2].

Several biological mechanisms through which sleep duration may lead to diabetes have been suggested including elevated evening cortisol level, increase in sympathetic tone which has an inhibitory effect on pancreatic function, reduction in leptin. Now we learn about the role of melatonin in the regulation of glucose homeostasis. Stay tuned, this may open new therapeutic opportunities for T2DM.

Single nucleotide transcription factor 7-like 2 (TCF7L2) gene polymorphisms in anti-islet autoantibody-negative patients at onset of diabetes

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Background: Genetic variants within the transcription factor 7-like 2 (TCF7L2) gene were associated with the development of T2DM in adults from various ethnic groups. The aim of this study was to evaluate whether single nucleotide polymorphisms (SNPs) of transcription TCF7L2 gene are associated with the development of islet autoantibody-negative diabetes vs. islet autoantibody-positive diabetes in young patients and whether these SNPs are associated with specific clinical phenotypes.

Methods: Two noncoding variants in the TCF7L2 gene, rs12255372 and rs7903146, were genotyped in 893 subjects less than age 25 at the onset of diabetes and normal controls.

Results: A total of 140 patients (15.7%) were negative for all islet autoantibodies. The allele and genotype frequencies of two SNPs showed that these are associated (odds ratio up to 4) with the development of diabetes in the autoantibody-negative diabetic cohort, but not in the autoantibody-positive diabetic cohort.

Conclusions: TCF7L2 T2DM susceptibility alleles are associated with islet autoantibody-negative but not autoantibody-positive new onset diabetes in young patients.

TCF7L2 belongs to a subfamily of TCF7-like high-mobility group box-containing transcription factors and maps to chromosome 10q25. The TCF7L2 gene product is part of the Wnt signaling pathway. Emerging new evidence, recently reviewed [3], reveals that Wnt signaling influences endocrine pancreas development and modulates mature β -cell functions including insulin secretion, survival and proliferation. TCF7L2 also modulates adipogenesis and regulates GLP-1 production. Among adults, TCF7L2 genes are associated with the development of T2DM diabetes.

With the increasing incidence of childhood obesity it would be helpful to know who those at high risk of developing T2DM are. Moreover, in a child with new onset diabetes and overlapping diabetes phenotype, additional tools to define the type of diabetes are often needed. To date, diagnosis of T2DM has been by exclusion, mainly those with negative antibodies for type 1 diabetes mellitus (T1DM) are diagnosed with T2DM. The key finding of this study was that TCF7L2 CT/TT genotypes can help distinguish between young subjects autoantibody-positive and autoantibody-negative diabetes patients.

Important for clinical practice: at-risk groups for prediabetes and type 2 diabetes mellitus

Association of intrauterine exposure to maternal diabetes and obesity with type 2 diabetes in youth: the SEARCH case-control study

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Background: The association between in utero exposure to maternal diabetes and obesity and T2DM in diverse youths was studied.

Methods: In the SEARCH case-control study, 79 youths with T2DM and 190 nondiabetic control youths aged 10–22 years were studied. In utero exposures to maternal diabetes and obesity were recalled by biological mothers.

Results: Youths with T2DM were more likely to have been exposed to maternal diabetes or obesity in utero than were nondiabetic control youths ($p < 0.0001$ for each). Exposure to maternal diabetes led to a 5.7-fold increase and exposure to maternal obesity to a 2.8-fold increased risk to T2DM in the offspring after adjusting for offspring age, sex, and race/ethnicity. Adjustment for other perinatal and socioeconomic factors did not alter these associations. When offspring BMI was added, the OR for the association between in utero exposure to obesity and T2DM was attenuated toward the null (OR 1.1 [0.5–2.4]). Overall, of T2DM in youths could be attributed to intrauterine exposure to maternal diabetes and obesity.

Conclusions: Intrauterine exposures to maternal diabetes and obesity are strongly associated with T2DM in youth. Prevention efforts may need to target, in addition to childhood obesity, the increasing number of pregnancies complicated by obesity and diabetes

Association between maternal diabetes in utero and age at offspring's diagnosis of type 2 diabetes

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Background: The age of diabetes diagnosis in youths who have a parent with diabetes by diabetes type and timing of diagnosis of the parent's diabetes in relation to the youth's birth were studied.

Methods: The cohort comprised SEARCH for Diabetes in Youth Study participants with a diabetic parent.

Results: Youths with T2DM were more likely to have a parent with either type 1 or T2DM (mother 39.3%, father 21.2%) than youths with type 1 diabetes (5.3 and 6.7%, respectively, $p < 0.001$ for each). T2DM was diagnosed 1.68 years earlier among those exposed to diabetes in utero than among those whose mothers' diabetes was diagnosed later ($p = 0.018$, controlled for maternal diagnosis age, paternal diabetes, sex, and race/ethnicity). Age at diagnosis of type 1 diabetes for youths with and without in utero exposure did not differ significantly. Paternal age at diagnosis of diabetes and its relation to child's birth were not associated with age at diagnosis of offspring.

Conclusions: T2DM was diagnosed at younger ages among those exposed to hyperglycemia in utero. Among youths with type 1 diabetes, the effect of the intrauterine exposure was not significant when controlled for the mother's age of diagnosis.

It has been said before that 'The fathers have eaten sour grapes, and the children's teeth are set on edge' [Jeremiah Chapter 31(28)]. Increased maternal pre-pregnancy weight [4] and increased gestational weight gain are associated with increased risk of offspring obesity [5]. Maternal weight loss by bariatric surgery prevents transmission of obesity to children [6]. Using data from the SEARCH study, a multicenter survey of youths with diabetes diagnosed before age 20 years, we now learn that exposure to maternal obesity was also associated with a 2.8-fold risk for T2DM in adolescents and that exposure to maternal diabetes in utero was associated with a 5.7-fold risk for T2DM in adolescents. Moreover, in a study limited to diabetic youths, T2DM was diagnosed in younger ages in those exposed to diabetic intrauterine environment, whereas no difference was observed in subjects with type 1 diabetes.

These studies are specifically interesting in light of emerging data on epigenetics and obesity. Epigenetics refers to changes in gene expression that are not caused by changes in the underlying DNA sequence, but rather in other mechanisms. Yet these changes may remain through cell divisions and therefore are trans-generational. DNA methylation is one of the mechanisms that enables to either switch 'on or off' gene expression. During differentiation of the early embryo there are potential 'critical windows' when environment could affect methylation. Nutrition during early life can affect DNA methylation.

The Agouti viable yellow (A^y) mouse is a model of genetic obesity. The A^y mice are hyperphagic, obese with a yellow coat because the agouti protein impairs both the satiety mechanism at the melanocortin 4 receptor and pigmentation in hair follicles. In this mice model, it has been recently demonstrated that maternal obesity causes trans-generational amplification of body weight [7]. This

trans-generational amplification of body weight can be prevented by a methyl-supplemented diet that induces DNA hypermethylation during pregnancy, suggesting epigenetic mechanisms involved in this process. Taken together, these data imply that assisting pregnant women to meet the recommended weight gain during pregnancy may be an important strategy for preventing pediatric obesity and T2DM.

Pre-teen insulin resistance predicts weight gain, impaired fasting glucose, and type 2 diabetes at age 18–19 years: a 10-year prospective study of black and white girls

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Background: The roles of pre-teen insulin resistance and insulin in weight gain and the development of IFG and T2DM were assessed.

Methods: In a prospective cohort study, body habitus and fasting insulin and glucose were measured in girls aged 9–10 and 18–19 years. Multiple 3-D diet records were collected.

Results: At age 18–19 years there were 5 incident cases of T2DM, 37 cases of IFG, and 597 non-cases. Baseline insulin, HOMA-IR, IFG, the change in HOMA-IR during follow-up, and baseline insulin $\times$ total caloric intake interaction predicted IFG and T2DM at age 18–19 years. In multivariate analyses, the 10-year change in homeostatic model assessment of insulin resistance (HOMA-IR) and the age 9–10 years HOMA-IR $\times$ percentage of calories from fat interaction were positive predictors of 10-year changes in BMI.

Conclusions: Pre-teen IFG, insulin resistance (and insulin), and rapidly increasing insulin resistance during adolescence identifies girls who are at greater risk of future IFG and T2DM. In addition, insulin resistance, interacting with high-fat diets, identifies girls who are at risk of greater weight gain. These findings could open avenues to primary prevention of obesity, IFG, and T2DM in children.

The interactions of hyperinsulinemia and obesity are complex. Many scientists believe that this is a case of the 'chicken or the egg' – hyperinsulinemia contributes to obesity, but obesity in turn worsens insulin resistance, leading to IFG and T2DM.

In this 10-year tracking study, factors that may predict obesity, central obesity, IFG and T2DM were studied. Elevated insulin levels at age 9–10 years and HOMA-IR were found to have a central role in predicting future obesity and impaired glucose metabolism. Moreover, the interaction of poor dietary intake, i.e. increased intake of fat calories with hyperinsulinemia, further increases the ability to identify those children who are at risk.

The ability to predict upcoming health problems and to take preventive steps is a key point in health care. The findings of this study may help clinicians to identify young children with poor eating habits and hyperinsulinemia and treat them intensively to prevent future morbidity.

Parental diabetes, pubertal stage, and extreme obesity are the main risk factors for prediabetes in children and adolescents: a simple risk score to identify children at risk for prediabetes

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Background: Prediabetes is defined as impaired fasting glucose (IFG) or impaired glucose tolerance, and its prevalence parallels the increase of obesity. However, it is unclear who the children that should be screened for prediabetes are.

Methods: The authors studied 437 overweight children and adolescents to identify risk factors for prediabetes. A risk score for prediabetes was calculated and examined in a second, independent cohort of 567 overweight youths. History of T2DM in parents and grandparents, degree of overweight, age, pubertal

stage, birth weight, hypertension, dyslipidemia, acanthosis nigricans, and abdominal obesity were considered as potential risk factors.

Results: The frequency of prediabetes was 6% in the first cohort and 17% in the second one. The strongest association was observed for history of parental diabetes with a 6.3- to 9.5-fold risk, followed by pubertal stage with a 5.5- to 6.2-fold risk and by extreme obesity with a 3.3- to 5.0-fold increased risk.

Conclusions: The main risk factors for prediabetes were parental diabetes, pubertal stage, and extreme obesity. Screening for prediabetes seems meaningful in subjects with either a parental history of T2DM or a combination of extreme obesity and pubertal stage and detected nearly 90% of the overweight children and adolescents with prediabetes.

According to recent data in 2003–2006 [8], 16.3% of children and adolescents aged 2–19 years were at or above the 95th percentile, and 31.9% were at or above the 85th percentile. In light of the increasing rates of obesity it is clear that strict criteria for those who need to be screened are necessary to separate the wheat from the chaff. The authors aimed to identify risk factor for prediabetes in overweight children and adolescents. In this study, overweight was defined as BMI above the 90th percentile, obesity as BMI above the 97th percentile and extreme obesity as BMI above the 99.5 percentile. Interestingly, potential predictors such as diabetes in grandparents, gender, birth weight, hypertension, dyslipidemia, acanthosis nigricans, and abdominal obesity were not significantly associated to prediabetes. The authors developed a risk score for OGTT of at least 2 points where parental diabetes scores 2 points, positive puberty scores 1 point, and extreme obesity score 1 point. This risk score had a sensitivity of 90%. These findings need to be studied in other ethnic populations, but it seems reasonable to screen only those with extreme obesity rather than those with overweight and to exclude history in grandparents. Another particularly high-risk population to target for screening recently described is overweight siblings of children diagnosed with T2DM. Siblings had 4 times greater odds of having abnormal glucose tolerance compared with other overweight children [9].

New concerns: reliability of our screening tools

Reproducibility of the oral glucose tolerance test in overweight children

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Background: The oral glucose tolerance test (OGTT) is used to test for diabetes, insulin resistance and the metabolic syndrome. The reproducibility of the test in overweight children was evaluated.

Methods: 60 overweight youths aged 8–17 years completed 2 OGTTs with an interval time between tests of 1–25 days. Insulin sensitivity was assessed by additional surrogate measures.

Results: Of the 10 subjects with impaired glucose tolerance (IGT) during the first test, only 3 (30%) had abnormal results during the second test. The percent positive agreement between the first and second OGTT was low for both impaired fasting glucose and IGT (22.2 and 27.3%, respectively). Fasting blood glucose had higher reproducibility compared with the 2-hour glucose. Obese youths with discordant OGTT results are more insulin-resistant.

Conclusions: These data show poor reproducibility of the OGTT in obese youths, in particular for the 2-hour plasma glucose.

Treating obesity is often futile, and in adolescents may carry the risk of developing eating disorders. Therefore, pediatricians need to select those patients who are at high risk for secondary morbidity of obesity. The metabolic syndrome is a cluster of physiologic markers including obesity, insulin resistance, dyslipidemia, and hypertension. The importance of the diagnosis of the metabolic syndrome is that it helps to identify those individuals at risk of developing diabetes and cardiovascular disease.

The definition established by the World Health Organization (WHO) diabetes group includes insulin resistance or its surrogates, IGT or diabetes as essential component. Similarly, the ADA recommends a fasting blood glucose method be used in obese children for screening. It is therefore essential to know the reliability of these tests. It is important to note that fasting indices represent different aspects of glucose homeostasis compared with indices derived from oral glucose stimulation. Fasting serum glucose levels reflect hepatic gluconeogenesis and basal pancreatic insulin release, while glucose levels after oral glucose stimulation reflect several different mechanisms including glucose absorption, gastrointestinal hormones, neural stimulation and pancreatic β -cell response. Among adults, longitudinal outcome studies of diabetes show worse outcomes in terms of cardiovascular morbidity and mortality in those diagnosed on the basis of the 2-hour plasma glucose result, as part of the OGTT. There is no clear-cut consensus on the role of OGTT in both clinical practice and research in children.

Reading this work we learn that the correlation and reproducibility of the 2-hour OGTT is worse than fasting glucose. Based on both OGTTs, 6 of 60 (10%) had IFG in the first test and 3 of 60 (5%) in the second test. Only 1 child had IFG in both tests. Based on both OGTTs, 10 of 60 (17%) had IGT in the first test and 12 of 60 (20%) in the second test. Only 3 children had IGT in both tests. This observation raises doubts about making a reliable diagnosis of glucose metabolism abnormalities outside diabetes. The OGTT is clearly less convenient, costs more and now we learn it is less reproducible, therefore fasting plasma glucose measurements should be preferred as a routine clinical test in children.

New concerns: complications in youths with T2DM

Macroalbuminuria and renal pathology in First Nation youth with type 2 diabetes

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Background: The prevalence of macroalbuminuria, clinical characteristics and renal pathological changes associated with macroalbuminuria were studied in a population of Canadian First Nation children and adolescents with T2DM.

Methods: In a retrospective chart review data on microalbuminuria (≥ 3 mg/mmol creatinine [26.5 mg/g]) and macroalbuminuria (≥ 28 mg/mmol creatinine [247.5 mg/g]), estimated glomerular filtration rate, renal pathology, and aggravating risk factors such as poor glycemic control, obesity, hypertension, glomerular hyperfiltration, hypercholesterolemia, smoking, and exposure to diabetes in utero were studied.

Results: Among 90 children and adolescents with T2DM, 53% had at least one random urine albumin-to-creatinine ratio consisting of the diagnosis of microalbuminuria at or within 8 years of diagnosis of diabetes. A total of 10 subjects had renal biopsies performed. None had classic diabetic nephropathy in biopsy. Nine of 10 exhibited immune complex disease or glomerulosclerosis.

Conclusions: This study suggests that the diagnosis of renal disease in children with T2DM cannot be reliably determined by clinical and laboratory findings and renal biopsy is necessary for accurate diagnosis.

There are only limited data regarding the microvascular complications of adolescents with T2DM. Initial reports from Pima Indians and Maori (New Zealand) with T2DM diagnosed during childhood demonstrate that microalbuminuria was present in up to one-fifth of the patients at diagnosis. After 10 years of follow-up, above 50% of the patients had microalbuminuria and 16% had macroalbuminuria. Studies comparing the prevalence of microalbuminuria in patients with childhood-onset T2DM and T1DM also suggest that adolescents with T2DM have more rapid progression of nephropathy.

This study by Seller and her colleagues teaches us that things are much more complicated than they look at first glance. They follow the Canadian First Nation children in whom the prevalence of T2DM in children aged 4–19 years is 1%.

Interestingly, Canadian First Nation children without diabetes have an increased rate of both congenital and acquired primary renal disease, mainly glomerulosclerosis. 90 youths with T2DM were studied. Their mean age was 15.2 years and mean duration of diabetes was 2.5 years (range 0.4–5). About one-third of them had microalbuminuria at diagnosis and more than half had at least one pathological test during follow-up. 10 subjects (9%) with persistent macroalbuminuria had renal biopsy. The biopsy results demonstrate that no one had sufficient histological changes to make a definitive diagnosis of diabetic nephropathy. Immune complex disease and glomerulosclerosis were the most common etiology of macroalbuminuria in this young population. These results are indeed surprising as nephropathy was intuitively thought to be secondary to poor control diabetes and obesity. Most interestingly, the population of the Canadian First Nation children has a private polymorphism in the hepatic nuclear factor (HNF)-1 α gene. This is a transcription factor expressed in many tissues including the liver, intestine, pancreatic β cells, and kidney. It appears that the HNF-1 α gene is associated with early-onset diabetes in this population and also is involved in the differentiation of the nephron and thus the authors speculated that this polymorphism may play a role in the development of the renal pathology found in this population. The effect of obesity on renal function and the impact of exposure to diabetes in utero are discussed. Most importantly, the authors conclude that diagnosis of renal disease cannot rely on laboratory findings and biopsy is necessary for accurate diagnosis.

Adolescents with type 2 diabetes: early indications of focal retinal neuropathy, retinal thinning, and venular dilation

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Background: The eye provides a unique window into the neural and vascular health of a patient with diabetes. The present study is the first of its kind to examine the neural retinal function, structure and retinal vascular health in adolescents with T2DM.

Methods: Focal neural responses were tested using multifocal electroretinography. Optical coherence tomography was utilized to measure retinal thickness. Digital fundus photographs were examined for the presence of retinopathy and to measure vascular caliber using retinal vessel analysis. 15 adolescents diagnosed with T2DM, aged 13–21 years with a mean diabetes duration of 2.1 ± 1.3 years, were tested and compared with 26 age-matched control subjects were also tested.

Results: Multifocal electroretinograms of the T2DM group were significantly delayed by 0.49 ms. The diabetic group also showed significant retinal thinning (10.3 μ m) and significant venular dilation (16.2 μ m).

Conclusions: The present study shows early indications of focal retinal neuropathy, retinal thinning, and venular dilation in adolescents with T2DM.

The present study is the first to examine structural and neural measures in eyes of adolescents with T2DM. Among adults with T2DM, vascular and neural changes in the eye occur before any documented vision change. Three different methods were performed: (1) Multifocal electroretinogram (mfERG), a noninvasive clinical tool which enables the recording of electrical potentials from multiple, small areas of the central retina and thus assesses retinal neuropathy. (2) Optical coherence tomography (OCT), a noninvasive, noncontact, transpupillary imaging technology which can image retinal structures and enables measurement of retinal thickness. (3) Digital fundus photographs for measuring vascular caliber. Abnormalities in the three parameters studied were demonstrated in adolescents with T2DM. Firstly, 40% of the subjects in the diabetes group presented with abnormal mfERG compared with 8% of the control subjects, and are thus considered to have functionally abnormal retinas. Secondly, retinal thickness of the diabetic group was thinner than that of the control group. Among adults with T2DM, changes in retinal thickness and nerve fiber are thought to be due to neural tissue loss. Finally, venular caliber of adolescents with T2DM was significantly larger than that of our control group. In adults, venular dilation has been associated with carotid artery disease, cerebrovascular disease, measures of atherosclerosis and diabetic nephropathy. The retinal changes in adolescent with T2DM were unexpected given the relatively short duration of diabetes. These data strengthen the recommendation of the ADA to study all adolescents with T2DM at diagnosis.

Structural and functional cardiac abnormalities in adolescent girls with poorly controlled type 2 diabetes

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Background: The main cause of death in adults with T2DM is cardiovascular disease. The cardiovascular status of adolescent-onset T2DM was studied.

Methods: Echocardiography and Doppler measurements were performed in 8 adolescents with T2DM, 11 with T1DM and 20 nondiabetic control subjects of whom 9 were lean and 11 overweight.

Results: Subjects with T2DM had larger left ventricular dimensions and left ventricular mass, which persisted when indexed to height. Diastolic filling was impaired in both diabetic groups, and systolic longitudinal function was lower in the T2DM group. Half of the group with T2DM met the published criteria for left ventricular hypertrophy and left ventricular dilatation, 25% had evidence of elevated left ventricular filling pressure in association with structural abnormalities.

Conclusions: This study has demonstrated preclinical abnormalities of cardiac structure and function in adolescent girls with T2DM, despite the short duration of diabetes and highlights the potential high cardiovascular risk occurring in adolescent T2DM.

This is the first study aimed to determine whether cardiac structural and functional abnormalities occur in adolescents with T2DM. Eight girls with T2DM, mean age of 14.9 ± 1.1 years, mean duration of diabetes 20 months and mean BMI 38.3 ± 7.4 kg/m², were studied and compared to age-matched T1DM, to lean and overweight control subjects. Studying cardiac structure, adolescents with T2DM had the largest heart reflected by left ventricular diameter, mass and left atrial area. This was significantly different from both lean and T1DM groups, but similar to the overweight group. Studying cardiac function, the T2DM subjects had lower diastolic and systolic longitudinal myocardial motion and higher left ventricular filling pressure. Only 1 of 8 patients with T2DM had no abnormalities compared to 10 of 11 subjects with type 1 diabetes. Based on these data, the authors hypothesized that these abnormal findings are related to obesity rather than diabetes per se and that diabetes further augmented cardiac abnormalities. The authors state that although the prognostic implications of the abnormalities detected are not known, they may progress toward clinical syndrome of heart failure. Recently, a 17-year-old male, whose weight was 140 kg, BMI 48 kg/m², who presented with a crushing pain radiating to the left shoulder and arm was reported [10]. He had elevated cardiac enzymes and was diagnosed with inferior myocardial infarction. No other risk factors for coronary artery disease were detected. The day is not far away when adolescents will leave the pediatrician's office with aspirin, antihypertensive medications and sublingual vasodilators. Adolescents with severe obesity, specifically those with T2DM, need routine cardiac evaluation. Intervention studies to prevent further progress of cardiac abnormalities are needed.

Clinical trials, new treatments: for prediabetes and for T2DM in adolescents

Short-term metabolic and cardiovascular effects of metformin in markedly obese adolescents with normal glucose tolerance

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Background: Metformin is an insulin sensitizer currently used as an adjunct to the treatment of some of the complications of childhood obesity besides T2DM. The metabolic and clinical effects of metformin in obese children with normal glucose tolerance were studied.

Methods: In a 4-month double-blind clinical trial in 28 obese adolescents with a mean BMI of 40.3 ± 5.7 kg/m², subjects were randomized to metformin (n = 15, dose 1,500 mg daily) or placebo (n = 13).

Results: The treatment with metformin was well tolerated and associated with a significant decreased BMI as well as with a reduction in subcutaneous fat, particularly the deep subcutaneous fat as assessed by magnetic resonance imaging. After intervention, the metformin group had a 35% improvement in insulin sensitivity compared with the placebo group. However, when adjusted for differences in baseline insulin sensitivity, significance was lost. While there was no change in inflammatory cytokines or lipid parameters, cardiovascular function as assessed by heart rate recovery after exercise improved with metformin and worsened in placebo.

Conclusions: Short-term use of metformin is well tolerated by obese children with normal glucose tolerance and has a beneficial effect on BMI and autonomic control of the heart as well as a trend toward improved insulin sensitivity. Thus, long-term treatment with MET may provide a means to ameliorate the cardiometabolic consequences of adolescent obesity.

This study is an additional contribution to several earlier works about the impact of metformin on weight loss and metabolic parameters in obese adolescents. As insulin resistance is a major player in comorbidities of obesity such as T2DM, hypertension and dyslipidemia, it seems logical to try to suppress elevated insulin levels to improve metabolic abnormalities. Moreover, studies among adults show a positive effect on weight loss. In this double-blind placebo-controlled intervention, the effects of metformin on metabolic parameters and fat partitioning were studied in obese children. In addition, an attempt to assess the effect of metformin on physiological measures of cardiovascular risk was taken. Heart rate recovery after exercise was studied after a self-paced exercise step test. During exercise there is a sympathetic dominance associated with increased heart rate. In the recovery period after exercise there is reactivation of parasympathetic tone with a drop in heart rate. A large drop in heart rate after exercise indicates an intact parasympathetic response whereas poor recovery rate has been associated insulin resistance and higher risk of developing T2DM. After 4 months those who were treated with metformin had: (1) a significantly lower BMI than the placebo group; (2) a reduction in deep subcutaneous fat; (3) an increase in heart rate recovery that paralleled the change in BMI, and (4) there was no change in lipid profile and CRP. Metformin treatment had short-term beneficial effects in obese children.

The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials

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Background: The effects of metformin, oral contraceptives (OCs), and/or lifestyle modification in obese adolescents with PCOS were studied.

Methods: A total of 79 obese adolescent women with PCOS were randomized to metformin, placebo, a lifestyle modification program, or OC. In the combined treatment trial, all subjects received lifestyle modification and OC and were randomized to metformin or placebo. Serum concentrations of androgens and lipids were measured.

Results: Lifestyle modification alone resulted in a 59% reduction in free androgen index with a 122% increase in SHBG. OC resulted in a significant decrease in total testosterone (44%) and free androgen index (86%) but also resulted in an increase in C-reactive protein (39.7%) and cholesterol (14%). The combination of lifestyle modification, OC, and metformin resulted in a 55% decrease in total testosterone, as compared to 33% with combined treatment and placebo, a 4% reduction in waist circumference, and a significant increase in HDL (46%).

Conclusions: In these preliminary trials, both lifestyle modification and OCs significantly reduce androgens and increase SHBG in obese adolescents with PCOS. Metformin, in combination with lifestyle modification and OC, reduces central adiposity, reduces total testosterone, and increases HDL, but does not enhance overall weight reduction.

This is a two-stage study on different treatment modalities of obese adolescent girls with PCOS. In a 'single treatment trial', 43 obese adolescent girls with PCOS were randomized to one of four arms: metformin, OC, lifestyle modification or placebo. Nine subjects did not complete the trial. In girls treated with OC there was a significant reduction in weight, in androgen levels, and in plasminogen activator inhibitor, however these positive changes were accompanied by an increase in CRP and LDL cholesterol. Lifestyle modification resulted in a significant reduction in androgens, in diastolic blood pressure and plasminogen activator inhibitor levels, however these were associated with compliance problems. Metformin treatment resulted in reduction in triglyceride levels with no change in BMI, fasting insulin or menstrual cycles. As OC and lifestyle modification resulted in improvement, the second stage study built was the 'combined treatment trial'. All 36 participants received lifestyle modification and OC, and were randomized to either metformin or placebo. While metformin did not induce weight loss it was associated with reduction in central obesity, albeit with significant increase in CRP levels. The importance of this study is that it increases the uncertainty of the benefits of different treatments. It seems that we fix one thing but break another. The bottom line as usual is that we need larger studies for a longer time.

Reversal of type 2 diabetes mellitus and improvements in cardiovascular risk factors after surgical weight loss in adolescents

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Background: T2DM is associated with obesity, dyslipidemia, and hypertension, all well-known risk factors for cardiovascular disease. Surgical weight loss has resulted in a marked reduction of these risk factors in adults. The impact of gastric bypass on metabolic dysfunction and cardiovascular risk in adolescents with T2DM was studied.

Methods: Eleven adolescents who underwent Roux-en-Y gastric bypass at 5 centers were studied. Anthropometric, hemodynamic, and biochemical measures and surgical complications were analyzed. Data were compared with 67 adolescents with T2DM who were treated medically.

Results: Adolescents who underwent Roux-en-Y gastric bypass were extremely obese with a mean BMI of 50 ± 5.9 kg/m² with numerous cardiovascular risk factors. After surgery there was evidence of remission of T2DM in all but 1 patient. Significant improvements in BMI (–34%), fasting blood glucose (–41%), fasting insulin concentrations (–81%), hemoglobin A_{1c} levels (7.3–5.6%), and insulin sensitivity were also seen. There were significant improvements in serum lipid levels and blood pressure. In comparison, adolescents with T2DM who were followed during 1 year of medical treatment demonstrated stable body weight and no significant change in blood pressure or in diabetic medication use. Medically managed patients had significantly improved hemoglobin A_{1c} levels over 1 year (baseline: $7.85 \pm 2.3\%$; 1 year: $7.1 \pm 2\%$).

Conclusions: Extremely obese diabetic adolescents experience significant weight loss and remission of T2DM after Roux-en-Y gastric bypass. Improvements in insulin resistance, β -cell function, and cardiovascular risk factors support Roux-en-Y gastric bypass as an intervention that improves the health of these adolescents. Although the long-term efficacy of Roux-en-Y gastric bypass is not known, these findings suggest that Roux-en-Y gastric bypass is an effective option for the treatment of extremely obese adolescents with T2DM.

According to the recently published guidelines of the Endocrine Society, bariatric surgery was suggested for adolescents who have reached their adult height with BMI ≥ 50 kg/m² or BMI ≥ 40 kg/m² with severe comorbidities in whom lifestyle modifications and/or pharmacotherapy have failed [11]. The Roux-en-Y anastomosis is named after César Roux, the surgeon who first described the method and the stick-figure representation. An estimated 2,700 adolescent bariatric surgeries were performed between 1996 and 2003 [12]. While there was only little variation in the annual case volume in adolescent bariatric surgeries between 1996 and 2000, the number more than tripled from 2000 to 2003. In 2007 the NIH launched a prospective study called Teen-LABS (Longitudinal Assessment of Bariatric Surgery) to help determine if bariatric surgery is appropriate for adolescents. The study is

planned for 5 years and we are waiting for data about obesity-related medical problems, other health risk factors, and quality of life before and after surgery. Meanwhile, we learn about the outcome of morbid obese adolescents with T2DM who underwent Roux-en-Y gastric bypass. The authors report that in addition to improved glycemic control, diabetic adolescents undergoing Roux-en-Y gastric bypass had significant improvements in measures of fatty liver disease, blood pressure, serum triglycerides, and total cholesterol. Among adults, T2DM was resolved in 77% of the patients and improved in 86% after bariatric procedures. Several antidiabetic properties are suggested [13], including decreased secretion of ghrelin, an exaggerated postprandial PYY response, contributing to appetite loss, and also increased glucagon-like peptide 1 (GLP-1) levels. One final point, based on 1 operated patient who did not experience resolution of diabetes even though at 3 years after surgery his BMI was reduced to 23 kg/m², the authors suggest that over time, there may be β -cell dysfunction that may not be recoverable even after bariatric surgery. Therefore, a greater benefit may be derived by reducing insulin resistance earlier in the course of T2DM to prevent β -cell fatigue, perhaps before the requirement of insulin therapy.

Food for thought: Medications increasing the risk for impaired glucose metabolism and T2DM

Metabolic and cardiovascular adverse events associated with antipsychotic treatment in children and adolescents

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Background: The metabolic disturbances and cardiovascular events in children and adolescents treated with antipsychotics were studied.

Methods: In a retrospective cohort design, a treatment cohort of 4,140 children and adolescents prescribed 1 of 5 atypical or 2 conventional antipsychotics, and a random sample of 4,500 children not treated with psychotropic medications were compared.

Results: Compared with the control sample, the treated cohort had a higher prevalence of obesity (odds ratio [OR] 2.13), T2DM (OR 3.23), cardiovascular conditions (OR 2.70), and orthostatic hypotension (OR 1.64). Patients exposed to multiple antipsychotics were at significantly higher risk for incident obesity/weight gain (OR 2.28), T2DM (OR 2.36), and dyslipidemia (OR 5.26). Cardiovascular events were more likely to occur in those treated with conventional (OR 4.34) or multiple (OR 1.57) antipsychotics and mood stabilizers (OR 1.31).

Conclusions: Antipsychotics are associated with several metabolic and cardiovascular-related adverse events in pediatric populations, especially when multiple antipsychotics or classes of psychotropic medications are co-prescribed, controlling for individual risk factors.

In the United States, prescriptions for atypical antipsychotic drugs for youths increased 500% from approximately 201,000 in 1993 to 1,224,000 in 2002. The majority of prescriptions of an antipsychotic were for nonpsychotic conditions including disruptive behavior disorders (37.8%), mood disorders (31.8%), pervasive developmental disorders or mental retardation (17.3%). Only 14.2% were given to schizophrenia and bipolar disorder [14]. According to IMS Health, a private firm that tracks drug trends, the overall sales of atypical antipsychotics drugs past all other classes, reaching USD 14.6 billion in 2008. Therefore the public health implications of wide off-label use of this class are so important.

In this study we learn that the odds of developing obesity, T2DM, or dyslipidemia were higher for girls, adolescents 13 years and older and those exposed to multiple antipsychotics. It took 2–3 years between initiation of antipsychotic therapy and the incident of comorbidity. Importantly, patients with preexisting obesity and hypertension had a 4.5-fold increased risk of developing T2DM.

Cardiovascular events, defined as myocardial infarction, ischemic pulmonary heart disease, cardiomyopathy and arrhythmias, were higher in those treated with conventional antipsychotics or exposed to multiple antipsychotics. Overall, 25% of the children and adolescents treated with antipsychotic treatment had 1–3 comorbid chronic medical conditions in addition to their psychiatric disorder. The authors should be commended for this important study. The current emerging evidence provides support that the benefits and risks of antipsychotic treatment should be weighted considering the possible toxic effects.

Effect of valproic acid treatment on body composition, leptin and the soluble leptin receptor in epileptic children

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Background: The aim of the study was to determine the influence of valproic acid treatment on leptin, the soluble leptin receptor (sOB-R), the sOB-R/leptin ratio, body composition and insulin resistance in epileptic children.

Methods: Body composition, glucose homeostasis, leptin levels, sOB-R and the sOB-R/leptin ratio were determined in a cross-sectional cohort study of children >6 years with idiopathic epilepsy treated with antiepileptic drugs for at least 6 months.

Results: 87 children were on treatment with VPA, and 55 on other antiepileptic drugs. VPA-treated children had significantly higher BMI standard deviation scores, body fat, serum insulin concentrations and homeostasis model assessment (HOMA) index. Leptin concentrations were significantly higher and the sOB-R/leptin ratio was significantly lower when compared to the non-VPA group. Overweight VPA-treated children showed lower sOB-R concentrations and a lower sOB-R/leptin ratio (each $p < 0.001$) as well as higher body fat and leptin levels (each $p < 0.001$) compared to lean VPA-treated children.

Conclusion: VPA monotherapy was associated with higher body weight, body fat and serum leptin concentrations as well as impaired glucose homeostasis. Low sOB-R concentrations and a low sOB-R/leptin ratio in overweight VPA-treated patients might contribute to disturbances in glucose homeostasis and to the development of the metabolic syndrome in these children later in life.

This is yet another group of children that needs special attention because of the increased risk to significant metabolic complications secondary to treatment. Epilepsy is one of the most common neurological diseases, and VPA is one of the most widely prescribed antiepileptic drugs. One of the most common side effects of VPA is weight gain. In addition, hyperinsulinemia and increased prevalence of polycystic ovary syndromes (PCOS) in women with epilepsy and different features of the metabolic syndrome were reported. In this study the authors aimed to characterize the influence of VPA treatment on the adipocytokine axis. In the current study, higher fat mass was not only demonstrated in overweight VPA-treated children but also in lean VPA-treated children compared to lean controls. Similarly, hyperleptinemia in VPA-treated children was independent of body weight. Thus, VPA modifies leptin levels through the increase of body weight. In addition, overweight VPA-treated children had higher leptin levels, a lower sOB-R and lower sOB-R/leptin ratio compared to lean VPA-treated patients, possibly contributing to disturbances in glucose homeostasis and the development of the metabolic syndrome.

Among adults, insulin resistance caused by antipsychotic agents and valproic acid was corrected with insulin sensitizers without compromising their psychotropic effect [15]. Studies aimed at assessing the efficacy of metformin in preventing VPA-induced weight gain and hyperinsulinemia in children are needed.

Hyperlipidemia

Important for clinical practice: guidelines for treating hyperlipidemia in children and adolescents

Dyslipidemia in youth with diabetes: to treat or not to treat?

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Background: Both T1D and T2D are increasing in youth and manifesting at younger ages, implying a longer burden of disease and earlier onset of vascular complications. Given that dyslipidemia is an important and potentially modifiable CVD risk factor, data for clinical decision-making regarding screening criteria and treatment of dyslipidemia in this high-risk population are of significant public health importance.

Methods: Recent data and current recommendations on dyslipidemia in youths with DM were reviewed.

Results: The authors emphasize that because no prospective data exist on safety, cost, or outcomes on dyslipidemia medications in adolescents with DM, it is uncertain how aggressively CVD risk factors should be treated in this population. Arguments against aggressive treatment include lack of data on safety, efficacy, and outcome, and even on surrogate marker data; intraindividual and interindividual variability; medication cost; potential life-long treatment, and data suggesting that early vascular lesions can regress with treatment in adulthood. Conversely, arguments for aggressive treatment include safety in adults with DM and in youth with familial hypercholesterolemia; data from landmark studies on the presence of early atherosclerosis in youth; increased risk of coronary heart disease in young adults with DM compared with nondiabetics; a preponderance of data indicating a reduced risk of coronary heart disease with statin treatment in adults; tracking of lipids from youth to adulthood.

Conclusions: Clinicians still need to adjust existing guidelines to individual patients and carefully weigh the possible benefits of treating cholesterol problems in children with diabetes against the safety, cost, and other concerns.

Recent studies have shown that cholesterol problems are widespread among children with diabetes. In the SEARCH for Diabetes in Youth Study, the prevalence of abnormal lipids was higher in T2DM than in T1DM: 33 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 cholesterol concentration <40 mg/dl [16]. Only 1% of those with T1DM and 5% of T2DM were receiving pharmacologic therapy for dyslipidemia.

As demonstrated in this review, the juries are still out on the intensity needed to treat children with diabetes and dyslipidemia. Two important concepts should be mentioned. The first one is lipotoxicity, i.e. the exposure of the β -cell to excessive levels of lipids may be a cause of worsening β -cell function. In this view, failure to correct hyperlipidemia dooms the β -cell to a continual assault that perpetuates the downward spiral to β -cell dysfunction and β -cell death [17]. In vitro, prolonged exposure of insulin-secreting cells to elevated levels of fatty acids is associated with poor insulin secretion, impairment of insulin gene expression, and apoptosis of the β cell. The second intriguing concept raised in this review is the possible negative 'vasculometabolic memory' analogous to that of 'metabolic memory' in diabetes. The idea of 'metabolic memory' is that early abnormal environment may be remembered in the target organ and may have persistent effects. In diabetes, good metabolic control, achieved early in the course of diabetes, substantially reduces development of microvascular complications. It is tempting to extrapolate this concept to abnormal lipids level as well. If so, it is possible that early treatment of dyslipidemia is necessary to prevent lifelong atherosclerosis.

Lipid screening and cardiovascular health in childhood

Daniels SR, Greer FR, et al: Committee on Nutrition
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Background: Given the current epidemic of childhood obesity with the subsequent increasing risk of T2DM, hypertension, and cardiovascular disease in older children and adults, there was a need of new guidelines.

Methods: A literature search designed to identify appropriate observational studies, clinical trials, reviews, meta-analyses and systematic reviews.

Results: The approach to screening children and adolescents with a fasting lipid profile remains a targeted approach. Overweight children belong to a special risk category of children and are in need of cholesterol screening regardless of family history or other risk factors.

Conclusions: For patients 8 years and older with an LDL concentration of ≥ 190 mg/dl, or ≥ 160 mg/dl with a family history of early heart disease or with two additional risk factors, pharmacologic intervention should be considered.

There was a big commotion after the publication of the new policy statement including editorials in leading medical journals [18, 19], daily newspapers, news and internet postings. The current guidelines still support targeted screening, i.e. children and adolescents with a positive family history of dyslipidemia or premature CVD (≤ 55 years of age for men and ≤ 65 years of age for women), children with unknown family history or those with other CVD risk factors, such as hypertension, cigarette smoking, or diabetes mellitus and the new inclusion of overweight and obesity. This targeted screening should take place after 2 years of age but no later than 10 years of age. The most controversial recommendations were pharmacologic intervention beginning at age 8 years and the inclusion of statins as first-line of pharmacological therapy. Repeated concerns were the paucity of long term efficacy and the poor long-term safety data in children and adolescents available to date. The response to concerns regarding the lack of strong evidence in terms of primary prevention of adult-onset CVD was that it is unlikely that such evidence will be available as these studies last for several decades.

Guidelines are recommendations for therapy, but they do not restrict therapeutic freedom.

The science of medicine should be supported by the 'art of care'. Each physician will need to decide for each child if and when pharmacological therapy is needed.

One final point, although no professional organization recommends universal screening, in a recent review by Kwiterovich [20] it was suggested that 'each child and adolescent should ideally have an assessment of their plasma lipids and lipoproteins'.

Spectrum and management of hypertriglyceridemia among children in clinical practice

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Background: The prevalence of hypertriglyceridemia in youths will likely increase as a consequence of childhood obesity and increased screening for dyslipidemias. Factors associated with increased triglyceride (TG) levels and treatment options were studied.

Methods: Clinical review of data for 76 patients who had at least one elevated TG level (>4 mmol/l [>350 mg/dl]) was performed.

Results: Hypertriglyceridemia was secondary to lifestyle factors in 17% of the patients. The rest had primary hypertriglyceridemia, with 43% having familial combined hypertriglyceridemia and hypercholesterolemia (type II), 33% having primary hypertriglyceridemia (type IV), 5% having familial lipase deficiency (type I), and 2% having hyperlipoproteinemia E2/E2 phenotype (type III). TG levels were highest in type I and III hypertriglyceridemia (>10 mmol/l [>900 mg/dl]). A total of 45% received drug therapy as part of TG level management (bile acid-binding resins, fibrates, statins). TG levels were found to decrease over time with the use of fibrates, to increase with the use of bile acid-binding resins, and not to change with the use of statins.

Conclusions: Lifestyle modifications remain the primary therapeutic avenue for the management of pediatric hypertriglyceridemia. An algorithm for the management of this heterogeneous population to guide clinicians in their treatment decisions is proposed.

This is a clinical experience of a single pediatric lipid disorder clinic over 33 years. During this time period, 76 children at a median age of 11.6 years (range 5.1–20.3) with hypertriglyceridemia were followed. Most patients were asymptomatic and were referred because of family history or by a routine examination. During their entire follow-up periods, almost half of the patients were given lipid-lowering medications. The authors report that the use of fibrates was associated with the most significant decrease in TG levels and that the use of statins did not affect TG level. TG levels increased with the use of bile acid-binding resins. According to a proposed algorithm the decision of treatment was based on TG levels. With TG levels between 150 and 450 mg/dl, lifestyle changes should be prioritized and ω -3 can be supplementary. With TG levels between 450 and 900 mg/dl, decision on treatment is dependent on a complete lipid profile. For isolated TG levels, fibrates should be considered whereas if LDL-C is elevated as well, statins should be considered. About one-fifth of overweight children have elevated TG levels so it appears that we will need to study the long-term impact of ω -3, diet and medication on TG levels.

Food for Thought

Mirthful laughter, as adjunct therapy in diabetic care, increases HDL cholesterol and attenuates inflammatory cytokines and HS-CRP and possible CVD risk

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Background: Psychosocial status has a role in maintaining health and preventing disease. The effect of ‘mirthful laughter’ on individuals with diabetes was studied.

Methods: A group of 20 high-risk diabetic patients with hypertension and hyperlipidemia were divided into two groups: laughter group and control group. Both groups were started on standard medications for diabetes, hypertension and hyperlipidemia. Subjects were followed for 12 months and levels of stress hormones epinephrine and norepinephrine, HDL cholesterol, inflammatory cytokines TNF, IFN, IL-6 and C-reactive proteins were measured. The laughter group viewed self-selected humor for 30 min in addition to the standard therapies described above.

Results: Patients in the laughter group had lower epinephrine and norepinephrine levels by the second month, suggesting lower stress levels. The laughter group also had lower levels of TNF, IFN, IL-6 and C-reactive protein levels, indicating lower levels of inflammation and increased HDL cholesterol. At the end of 1 year, the research team saw significant improvement in the laughter group: HDL cholesterol had risen by 26% compared with and only 3% in control group. Harmful C-reactive proteins decreased 66% in the laughter group vs. 26% for the control group.

Conclusion: The study suggests that the addition of an adjunct therapeutic mirthful laughter Rx (a potential modulator of positive mood state) to standard diabetes care may lower stress and inflammatory response and increase good cholesterol levels.

The first and last abstract of this chapter speak for themselves. Finally positive messages: sleep more and have a mirthful laughter –your weight and cardiovascular risk factors will improve.

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