Obesity and Weight Regulation

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Once more, the recent literature on obesity and weight regulation demonstrates the activity and interest of this field of science. For the *Yearbook* selection this year, only articles published in journals with a high impact factor were considered, assuming that relevant findings were published in these journals.

New concerns

Childhood body mass index and the risk of coronary heart disease in adulthood

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N Engl J Med 2007;357:2329–2337

Background: Although obesity in childhood and adolescence is considered to be one of the major health problems in this age group, only a few studies have investigated its long-term outcome. The severity of the long-term effects of childhood obesity on coronary heart disease (CHD) especially remains unknown.

Methods: In the Danish schoolchildren cohort consisting of more than 270,000 children, height and weight have been measured and the association between body mass index in childhood and CHD in adulthood investigated. CHD events were ascertained by linkage to national registers.

Results: The risk of a CHD event (non-fatal and fatal) among adults was positively associated with BMI at 7–13 years of age for boys and 10–13 years of age for girls. The risk increased across the entire BMI distribution. Adjustment for birth weight strengthened the results.

Conclusion(s): Higher BMI during childhood is associated with an increased risk of CHD in adulthood. The findings presented here suggest that as children are becoming heavier in many countries, the numbers of children at risk for developing CHD in adulthood increases in parallel.

Adolescent overweight and future adult coronary heart disease

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N Engl J Med 2007;357:2371–2379

Background: Although obesity in childhood and adolescence is considered to be one of the major health problems in this age group, only a few studies have investigated its long-term outcome. Especially the severity of the long-term effects of childhood obesity on coronary heart disease (CHD) remains unknown.

Methods: The prevalence of 35-year-old persons with obesity in the year 2020 was estimated on the basis of recent prevalence data and historical trends regarding overweight adolescents becoming obese in adulthood. In the next step the so-called CHD Policy Model was used to project the annual excess incidence and prevalence of CHD, the total number of excess CHD events, and the death rates from CHD.

Results: A significantly increased prevalence of obesity in 35-year-olds was projected in the year 2020. As a consequence of this, an increase in the incidence of CHD is projected to occur in young adults. In the year 2035 it is estimated that the prevalence of CHD will increase by 5–16%. More than 100,000 excess cases of CHD will be attributable to the increased obesity. Further computer simulations show

that even when aggressive treatment will be applied, the projected increases in number of CHD events will be reduced but not eliminated.

Conclusion(s): Although there are several limitations to computer simulations and projections of 25 or more years into the future, the present analysis nevertheless strongly suggests that adolescence overweight will increase the rates of CHD in young and middle-aged adults in the near future.

There are only a few good long-term follow-up data on the relationship between BMI in adolescence and adult morbidity and mortality. Since mortality during early and middle adulthood is low, a large number of subjects and a long-term follow-up period are necessary and a clear definition of comorbidities or endpoints as well as a standardized documentation. In the study of Baker et al., a very large population-based cohort of children has been studied. It has been found that higher childhood BMI values elevated the risk of having a CHD event in adulthood. The large size of the study group gave the statistical power to investigate the effects of childhood BMI separately in relation to sex and age. Children today are heavier than in the past. In many Western countries there are no signs that the increases in childhood obesity are slowing down. The linear association between childhood BMI and adult CHD identified in this study suggests that more children than ever before are facing increased risks of CHD in adulthood. A child's probability of having a future CHD event could be calculated on the basis of the present study as follows: a 13-year-old boy who weighs 11.2 kg more than average will have a 33% increase in the probability of having a CHD event before the age of 60 years.

The article of Bibbins-Domingo et al. supports the fear articulated by Baker et al. by means of computer simulation using the CHD Policy Model. It is a model to estimate the incidence, prevalence, mortality and the costs associated with CHD in US residents who are 30 years old or older.

Projections 25 years or more into the future are of course problematic because many factors that are important may change in the mean time. Nevertheless, the present calculations seem to be robust. They show that significant morbidity and mortality begin in young adulthood resulting in more than 100,000 excess cases of CHD by 2035, even with the most modest projection of future obesity.

On the other hand, the present assumptions may be too conservative. It is not possible to estimate the effect of the early atherogenesis that may already occur in children as a result of their overweight. It has been shown that cardiovascular risk factors are elevated already in young children. These are markers for atherosclerotic disease and it has also been shown that atherosclerosis may start early in obese children. Therefore the estimates for disease rates in adults as a consequence of this process may be even underestimated [1].

Early development of visceral fat excess after spontaneous catch-up growth in children with low birth weight

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Background: Prenatal growth restriction increases the risk of obesity and metabolic syndrome in adulthood. The development of these sequelae is associated with infantile catch-up of weight and hyperinsulinemic obesity at the age of 4 years.

Methods: 22 children born appropriate for gestational age (AGA) and 29 children born small for gestational age (SGA) were studied longitudinally (from age 2 to 6) concerning auxiological, endocrine, and metabolic changes. Special emphasis lay on progression of weight changes between the age of 4–6 years and accumulation of visceral fat at the age of 6 years (assessed by magnetic resonance imaging).

Results: Between 2 and 6 years, SGA children showed an increase in insulin and IGF-I levels and neutrophil to lymphocyte ratio compared to AGA children. Even after the age of 4 years, SGA children showed a further increase in BMI and fat mass. At the age of 6, their visceral fat mass was increased by 50% compared to AGA children ($p < 0.005$). 62% of this increase was explained by changes in fasting insulin between 2 and 6 years ($\beta = 0.4$; $p < 0.0001$) and weight z-score between birth and age 2 years ($\beta = 0.53$; $p < 0.0001$).

Conclusion(s): Already at the age of 6 years, SGA children with catch-up growth show an excessive accumulation of visceral fat. Therefore, prevention of metabolic syndrome after prenatal growth restriction has to be advanced into prepubertal childhood.

Although the connection between low birth weight and metabolic syndrome in adulthood has been well known for some time by now [2], the mechanisms behind this association are not fully understood. As visceral fat has a different endocrine activity from subcutaneous fat, accumulation of visceral fat might be an important factor. In a previous study, a connection between low birth weight and increased visceral fat could be shown for prepubertal African-American children, but not for Caucasian-American children [3]. The above-mentioned article is the first to prove such an association between intrauterine growth restriction and the amount of visceral fat in prepubertal Caucasian children. In addition, the researchers were able to elucidate some of the factors contributing to the increased fat accumulation, though the causality of this association has yet to be determined.

Mechanism of the year

Neuropeptide Y acts directly in the periphery on fat tissue and mediates stress-induced obesity and metabolic syndrome

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Nat Med 2007;13:803–811

Background: Stress has been linked to the pathogenesis of many diseases, however its mechanism of action and role as a risk factor remains unclear. This has also been true so far for the well-established association between stress and obesity, abdominal fat distribution and the metabolic syndrome.

Methods: The authors investigated the role of neuropeptide Y (NPY) in the stress and hypocaloric diet-associated weight gain by use of in vitro models (3T3-L1 preadipocyte cells), in vivo models (animals) and by use of human adipose tissue samples, human fat implantation studies, and cold-induced stress studies.

Results: In summary, the study shows that stress exaggerates diet-induced obesity through a peripheral mechanism in the abdominal white adipose tissue that is mediated by NPY. Stressors such as exposure to cold or aggression lead to the release of NPY from sympathetic nerves. This leads to an up-regulation of NPY and its Y2 receptors in abdominal fat. This up-regulation is glucocorticoid-dependent. This positive feedback response by NPY leads to the growth of abdominal fat. This also leads to a stimulation of fat angiogenesis and macrophage infiltration. Pharmacological inhibition or fat-targeted knock-down of NPY2 receptor is antiangiogenic and antiadipogenic, while reducing abdominal obesity and metabolic abnormalities.

Conclusion(s): The findings of this study provide evidence that stress is not ‘just in the mind’ but rather affects body weight and metabolism by activating neurogenic angiogenesis and fat remodeling through an NPY-NPY2-receptor-dependent pathway that is localized in the white adipose tissue.

One type of obesity, mainly abdominal or visceral obesity, is linked to the metabolic syndrome and has an increased risk for cardiovascular diseases and diabetes. This type of obesity has also been linked to stress. In spite of the perceived association between stress and obesity, the nature of the relationship remains uncertain. Interestingly some people lose weight when stressed, whereas others gain weight. Although there is much evidence that stress and obesity are related to the hypothalamic control of food intake and metabolism, little has so far been known about the peripheral processes by which stress affects obesity.

Stress stimulates sympathoadrenomedullary activity, which is responsible for fight-or-flight responses. It is also the body's main mechanism of weight loss, acting through β -adrenoceptor-mediated lipolysis and inhibition of adipocyte proliferation in white adipose tissue, and stimulation of thermogenesis in brown adipose tissue. Paradoxically, sympathetic activity seems to be increased in obese humans, indicating that β -adrenergic activity might compensate for other factors that promote weight gain. One such factor is neuropeptide Y, a peptide derived from the brain and sympathetic nerves that has potent orexigenic activity, favoring the intake of carbohydrate-rich foods.

This study has shown, for the first time, the importance of the sympathetic neural transmitter NPY in adipose tissue remodeling and its role in stress-induced augmentation of diet-induced obesity and metabolic syndrome.

The proposed mechanism of stress-induced exacerbation of abdominal diet-induced obesity by activation of adipose tissue NPY-NPY2 receptor pathway is shown in the figure 1.

New mechanisms

Retinaldehyde represses adipogenesis and diet-induced obesity

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Nat Med 2007;13:695–702

Background: Retinoic acid is the most studied metabolite in the vitamin A pathway. It exerts a broad range of biologic effects, mainly by controlling gene expression. Retinoic acid is formed solely from retinaldehyde (Rald), which in turn is derived from vitamin A. Rald currently has no defined biological role outside the eye.

Methods: By means of in vitro and in vivo studies, the authors investigated the physiological role of Rald.

Results: Rald is present in rodent fat. The concentration in white fat ranged from 100 nM to 1 μ M. Rald binds to retinol-binding proteins (CRBP1, RBP4) and inhibits adipogenesis and suppresses peroxisome proliferator-activated receptor- γ and RXR responses. The in vitro studies showed that mice lacking the Rald-catabolizing enzyme retinaldehyde dehydrogenase 1 (Raldh 1) are resistant to diet-induced obesity and insulin resistance and showed increased energy dissipation. Furthermore, in *ob/ob* mice, treatment with Rald or Raldh inhibitor reduced fat and increased insulin sensitivity.

Conclusion(s): These studies show that Rald plays a distinct metabolic role in adipocyte differentiation in vitro, and in diet-induced insulin resistance and obesity in vivo.

Retinaldehyde, a vitamin A metabolite, has been previously thought to be active only in the visual system. The present studies now show that this molecule regulates adipogenesis and is possibly also able to improve insulin sensitivity. The studies show that Rald is present in fat at nanomolecular concentrations (~ 1 nM/g) and can interact with CRBP1 and RBP4, binding proteins involved in intracellular and circulating retinoic transport. Taken together, this data identifies Rald as a biologically active metabolite present in fat that regulates adipogenesis through its action on RXR and PPAR- γ responses. These effects are in opposite to the action of retinoic acid.

Vitamin A is a fat-soluble vitamin provided by the diet (e.g. by milk, liver and eggs) and also in form of some carotinoids such as found in carrots or red pepper. Vitamin A deficiency mainly occurs under malnutrition and is a major cause for blindness, weak immune system and developmental problems in developing countries. Furthermore, it has been shown that the vitamin A status influences the development and function of adipose tissue in whole animals. For example, low vitamin A status favors increased fat deposition [4]. Retinoic acid also influences adipocyte differentiation in cell culture. Ziouzenkova et al. show however that retinaldehyde is a naturally occurring signaling molecule in fat tissue, with its own distinct effects independent of retinoid acid formation and with important metabolic properties.

Fig. 1. The proposed mechanism of stress-induced exacerbation of abdominal diet-induced obesity by activation of adipose tissue NPY-PPY2 receptor pathway (modified according to Kuo et al., 2007).

Food for thought

Variations in *PPARD* determine the change in body composition during lifestyle intervention: a whole-body magnetic resonance study

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Background: The nuclear hormone receptor peroxisome proliferator-activated receptor-δ gene is an important regulator of lipid and energy metabolism in adipose tissue and skeletal muscle. Genetic variation in the *PPAR-δ* gene is reported to affect the insulin sensitivity. Based on *PPAR-δ* function in mitochondrial

oxidative pathways and muscle fiber composition, it is hypothesized that genetic variation in PPAR- δ might confer altered susceptibility towards the beneficial effects of aerobic exercise on insulin sensitivity and body composition.

Methods: 156 subjects at an increased risk for type 2 diabetes were genotyped and participated in a lifestyle intervention program. Body fat has been quantified using magnetic resonance spectroscopy and imaging.

Results: With regard to body composition, carriers of the minor SNP alleles of PPAR- δ displayed reduced responses to lifestyle intervention in terms of reduction in adipose tissue mass and increase in muscle volume. These changes were less pronounced in homo- and heterozygous carriers of the minor alleles as compared with homozygous carriers of the major alleles.

Conclusion(s): SNPs rs1053049, rs6902123 and rs2267668 in PPAR- δ affect lifestyle intervention-induced changes in fat mass and relative muscle mass.

In this study it has been demonstrated that genetic variation in PPAR- δ negatively affects the lifestyle intervention-induced changes in relative muscle volume, fat mass as well as ectopic fat storage in liver. The results suggest that individuals carrying the minor alleles of the tested PPAR- δ SNPs benefit from exercise and weight loss to a lesser extent. These findings would also be a mechanistic explanation for the additional findings of this study which show that these subjects had also reduced aerobic physical fitness and insulin sensitivity. Although PPAR- δ is expressed in many tissues, it is likely that SNPs in PPAR- δ exert the effects directly in skeletal muscle where expression reaches highest levels. These SNPs may affect fat mass as a consequence of altered muscle metabolism (e.g. altered myocellular β -oxidation). This study is especially interesting since the authors used a whole-body magnetic resonance approach to demonstrate that lifestyle intervention increases relative muscle volume with favorable effects on insulin sensitivity and hepatic lipid content. By doing this they could show that genetic variation in PPAR- δ was negatively associated with the effects on lifestyle intervention-induced changes in body composition.

Food for thought – in the true sense of the word

Leptin replacement alters brain response to food cues in genetically leptin-deficient adults

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Background: Leptin, the primary signal hormone from adipocyte energy stores, regulates feeding behavior and energy expenditure. Leptin replacement in leptin-deficient patients normalizes the increased body weight and the disturbed eating behavior. However, the neural circuits mediating these changes are unknown.

Methods: Three adults with leptin deficiency and morbid obesity have been studied using functional magnetic resonance imaging during presentation of food cues to these subjects.

Results: Leptin supplementation reduced the activation of the brain in regions linked to hunger (insula, parietal and temporal cortex) during viewing of food-related stimuli. In addition, leptin replacement led to an enhanced activation in regions linked to inhibition and satiety (prefrontal cortex).

Conclusion(s): These data show by functional magnetic resonance imaging that leptin replacement in leptin-deficient patients alters brain response to food cues.

Leptin regulates striatal regions and human eating behaviour

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Science 2007;317:1355

Background: Leptin, the primary signal hormone from adipocyte energy stores, regulates feeding behaviour and energy expenditure. Leptin replacement in leptin-deficient patients normalizes the increased body weight and the disturbed eating behaviour. However, the neural circuits mediating these changes are unknown.

Methods: A 14-year-old boy and a 19-year-old girl with congenital leptin deficiency, before and after 7 days of treatment with recombinant human leptin, were studied using functional magnetic resonance imaging. Brain activation was induced by visual images of food compared with images of non-food. Visual analogue scores were used to rate hunger, satiety, and the 'liking' of food images.

Results: After leptin treatment, hunger ratings decreased and satiety following a meal increased. Leptin-deficient patients showed a marked activation in the anteromedial ventral striatum (nucleus accumbens and caudate nucleus) and posterolateral ventral striatum (putamen and globus pallidus) when visual images of food were presented. The hunger-reducing effect of leptin in the leptin-deficient patients was accompanied by a region-specific change in the evoked neural response after leptin treatment. The ventral striatum (localized to nucleus accumbens-caudate nucleus) was identified as the site of an interaction between stimulus type, fasting state, and leptin.

Conclusion(s): Leptin markedly affects neural responses to visual food stimuli. Leptin administration in leptin-deficient patients results in an increased ability to discriminate between the rewarding properties of food and, at the neuronal level, in the modulation of activation in the ventral striatum.

Both articles support the idea that leptin acts on neural circuits governing food intake to diminish perception of food reward while enhancing the response to satiety signals generated during food consumption. The performed experiments provide insight into the neuroanatomical functions which are important for the effect of leptin. Functional magnetic resonance imaging is presented as a useful technique to answer these research questions. Although these results were found in rare cases of genetic leptin deficiency, they can provide understanding of normal leptin physiology and may help to identify new targets for the treatment of obesity.

Concepts revised

Thematic review series: adipocyte biology. Sympathetic and sensory innervation of white adipose tissue

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Background: Significant evidence has been brought up by the current literature that circulating factors, such as leptin, may serve as afferent signals to the brain informing it of body fat levels and the amount of energy stored. There is only little knowledge about efferent signals regulating peripheral adipose tissue and energy stores by the central nervous system. There are several data which show that the adrenal medullary organ by means of epinephrine (EPI) secretion regulates mobilization of lipids from white adipose tissue.

Results: This review suggests that in addition to the above-mentioned factors, the innervation of white adipose tissue is important for its regulation, especially in terms of lipid mobilization. The authors show that there is strong neurochemical (norepinephrine turnover), neuroanatomical (viral tract tracing), and functional (sympathetic denervation-induced blockade of lipolysis) evidence for the role of the sympathetic nervous system in lipid mobilization.

Conclusion(s): This review suggests that and explains how lipid mobilization occurs primarily through the sympathetic innervation of white adipose tissue.

There are several overviews on the role of the sympathetic nervous system in lipid mobilization which have been published recently [5, 6]. During the study of the reversal of seasonal obesity in Siberian hamsters, the authors found an interaction between receptors for the pineal hormone melatonin and the sympathetic nervous system outflow from brain to white adipose tissue. This ultimately led them to conclude that the sympathetic nervous system innervation of white adipose tissue is the primary initiator of lipid mobilization in these as well as other animals, and also in humans. This review summarizes the existent evidence of the role of the sympathetic nervous system in controlling lipid mobilization from white adipose tissue. It thereby adds an important physiological system by which afferent signals may regulate energy storage and mobilization by the control of the central nervous system. There are still more physiological pathways involved in the efferent regulation of adipose tissue mass. Experimental data support this idea also in terms of control of adipocyte number [7].

New genes

Evidence of an influence of a polymorphism near the INSIG2 on weight loss during a lifestyle intervention in obese children and adolescents

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Diabetes 2008;57:623–626

Background: Insulin-induced gene 2 (INSIG2) encodes a protein of the endoplasmic reticulum involved in cholesterol and fatty acid synthesis as well as in lipogenesis aiming at reducing lipogenesis and blocking differentiation of adipocytes. Recently a common genetic polymorphism in INSIG2 (rs7566605) was shown to be associated with an increased obesity risk for CC homozygotes [8].

Methods: This polymorphism has been genotyped in 293 obese children who have been enrolled in a 1-year intervention program for weight reduction.

Results: Patients with the CC genotype showed a lower reduction in their SDS BMI than patients with GC or GG genotype after 1 year. No association of this polymorphism with the cardiovascular risk factor profile could be found.

Conclusion(s): CC homozygotes at SNP rs7566605 in the INSIG gene lost less weight in a lifestyle intervention program as compared to the GC or GG genotypes.

This is the first study showing that an earlier described polymorphism in the vicinity of the INSIG2 gene is associated with weight loss during lifestyle intervention program. This SNP is located upstream of the transcriptional start site of the INSIG2 gene. Therefore it is unlikely that the SNP itself is functional. In the view of the still unknown function of this genetic variation and several scientific correspondences related to the initial description of this common genetic variance in *Science* [8] which all have failed to support the main finding of the original study, more studies are needed to elucidate the role and significance of this polymorphism near the INSIG gene on body weight regulation in men.

Hyperphagia and early-onset obesity due to a novel homozygous missense mutation in prohormone convertase 1/3

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Background: To achieve biological activity, many pro-hormones have to be cleaved by pro-hormone convertases. Deficiency in the pro-hormone convertase PC1/3 causes reduced cleavage of a wide variety of

pro-hormones, including pro-insulin, pro-glucagon and pro-opiomelanocortin, which leads to a rare syndrome combining obesity, intestinal dysfunction and dysregulation of glucose metabolism.

Methods: A novel homozygous missense mutation Ser307Leu was identified in the worldwide third patient with PC1/3 deficiency. Clinical phenotype and functional properties of the mutation were examined.

Results: The patient first presented with neonatal onset enteropathy, later he displayed severe obesity with hyperphagia (assessed via ad libitum test meal). As expected, low serum cortisol levels were accompanied by normal ACTH levels and high ACTH precursors and the patient showed a high pro-insulin/insulin ratio. Western blotting revealed a reduced but not completely abolished autocatalytic activity (pro-peptide cleavage, carboxyterminal processing) of the mutated PC1/3 enzyme, while no enzymatic processing of other substrates by the Ser307Leu mutant could be seen.

Conclusion(s): The severe obesity in PC1/3 mutations is mainly due to an increased energy intake. Patients with this mutation may show intractable diarrhoea as the first presenting feature.

Monogenic mutations are rare causes of obesity. However, they help us to increase our knowledge about the pathophysiology of obesity. In some cases, diagnosis of a monogenic disease might even imply a treatment option.

In PC1/3 deficiency, a high pro-insulin/insulin ratio is suggestive of the diagnosis. As this is an easy performable examination, determining this ratio should be considered in any patient with early-onset obesity, especially in the presence of intestinal dysfunction. PC1/3 has numerous substrates that are involved in energy homeostasis. Most likely, disrupted pro-opiomelanocortin processing is the main factor leading to hyperphagia in PC1/3 deficiency.

Interestingly, in this case report, neonatal diarrhea was the first presenting feature. Diarrhea is probably due to reduced activity of intestinal hormones such as cholecystokinin and glucagon-like peptides. As mutations in PC1/3 have only been described very recently [9], the prevalence of this disease is yet unknown. If more patients become identified, PC1/3 mutations might also prove to be an important differential diagnosis for neonatal diarrhea.

Genetics: from fused toes in mice to human obesity

A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity

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Science 2007;316:889–894

Background: Despite the fact that obesity is a serious international health problem, the genetic factors predisposing to obesity are poorly understood.

Methods: A genome-wide search for type 2 diabetes-susceptibility genes was performed comparing 1,924 UK type 2 diabetes patients and 2,938 UK population controls.

Results: A common variant in the FTO (fat mass and obesity-associated) gene was shown to predispose to diabetes through an effect on BMI (body mass index). This finding was replicated by genotyping 38,759 individuals in total. The 16% of homozygous adults for the risk allele weighed ~3 kg more. Compared with those who did not inherit a risk allele, they had 1.67-fold increased odds of obesity. This association was observed from age 7 years upward reflecting a specific increase in fat mass.

Conclusion(s): There is a strong association between variants in the FTO gene and obesity. Further studies are needed to provide insights into novel pathways involved in the control of adiposity.

Variation in FTO contributes to childhood obesity and severe adult obesity

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Nat Genet 2007;39:724–726

Background: Although common obesity has a strong genetic compound, there is still little knowledge on the underlying genetic causes.

Methods: 48 SNPs in different intergenic regions were tested in order to estimate the distribution of neutral SNPs in their case-control obesity sample from France and Canada.

Results: A set of SNPs was identified in the first intron of the FTO (fat mass and obesity-associated) gene on chromosome 16q12.2 that is consistently strongly associated with early-onset and severe obesity in both adults and children with an experiment-wise p value of 1.67×10^{-26} in 2,900 affected individuals and 5,100 controls. The at-risk haplotype yields a proportion of attributable risk of 22% for common obesity.

Conclusion(s): The authors conclude that FTO contributes to obesity and may be a target for subsequent functional analyses.

Obesity is an etiologically complex state reflecting the outcome of variations in a number of biochemical, physiological, and behavioral systems, some causal but, no doubt, others compensatory. The FTO seems to become the Holy Grail in the genetics of common obesity. Indeed, both above-mentioned studies surely represent the first true genetic signal for common obesity in adults and children and many other studies reproducing the original findings have followed. However, the mechanisms by which variants in FTO lead to obesity are still unknown. The gene is expressed in most tissues, including brain, pancreatic islets and adipose tissue. Functional studies are urgently needed to understand the molecular mechanism by which variants in FTO influence the risk of obesity.

Clinical trials

Effects of a weight management program on body composition and metabolic parameters in overweight children – a randomized controlled trial

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Background: Although the epidemic of childhood obesity and subsequently high prevalence rates of early manifest metabolic complications have been increasingly recognized as a major public health challenge over the last decade, reliable information on successful treatment strategies is still sparse.

Methods: A sample of 209 overweight (BMI >95th percentile) children aged 8–16 years were included in a randomized controlled trial. The control group received clinical counseling every 6 months, and the intervention group received a multidisciplinary family-based program consisting of nutrition, behavior modification, and exercise (biweekly for the first 6 months, bimonthly thereafter). A second randomization assigning participants to a structured meal plan intervention was discontinued due to high dropout rate.

Results: After 6 months, a significant reduction of weight, BMI, body fat mass, total cholesterol, fasting insulin and insulin resistance (HOMA-IR index) could be achieved in the intervention group compared to controls. At 12 months, these beneficial changes were sustained in the intervention vs. control group, e.g. BMI was reduced by 1.7 kg/m^2 vs. a gain of 1.6 kg/m^2 in controls, body fat mass (-3.7 vs. $+5.5 \text{ kg}$), cholesterol (-9.2 vs. $+3.7 \text{ mg/dl}$), and HOMA-IR (-1.52 vs. $+0.9$).

Conclusion(s): The study demonstrates the effectiveness of an intensive multidisciplinary weight management program in enhancing body composition and reducing insulin resistance over a time period of 12 months.

Twelve-month effectiveness of a parent-led, family-focused weight-management program for prepubertal children: a randomized, controlled trial

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Pediatrics 2007;119:517–525

Background: While most published evidence on the successful implementation of child weight management interventions is derived from studies in obese adolescents, much less is known about feasible treatment strategies for obesity in prepubertal children. The aim of the present study was to evaluate the effectiveness of a parenting-skills training for the treatment of obese children.

Methods: 111 (64% female) overweight, prepubertal children aged 6–9 years were included in an assessor-blinded, randomized, controlled trial. Participants were assigned to parenting-skills training plus lifestyle education, parenting-skills training alone, or a 12-month wait-listed control.

Results: After 12 months of treatment, BMI z-score was reduced by -0.24 with parenting-skills training plus lifestyle education vs. -0.15 with parenting skills alone and -0.13 with wait-listing for intervention. Reductions of BMI and waist circumference z-score were significantly greater in boys compared with girls. No differences in cardiovascular risk parameters (amongst others blood pressure, serum lipids, fasting insulin) between baseline and 12 months were observed.

Conclusion(s): Parenting-skills training combined with family lifestyle modification may be a valuable approach to weight management in prepubertal overweight children.

Efficacy of maintenance treatment approaches for childhood overweight: a randomized controlled trial

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Background: Lifestyle interventions are the most well-established interventions for childhood obesity. Although there is accumulating evidence for the short-term effectiveness of lifestyle modification, the long-term efficacy of such treatment programs in maintaining weight loss remains an area of uncertainty.

Methods: 204 overweight and obese 7- to 12-year-olds were enrolled in a 5-month family-based weight loss intervention. At 5 months, 150 were randomized to 1 of 3 maintenance treatments, i.e. 4 months of behavioral skills maintenance, social facilitation maintenance, or the control group. Primary outcome measures were BMI z-score and percentage overweight measured at completion of maintenance treatment, and 1 and 2 years following randomization.

Results: Weight maintenance in children receiving behavioral skills maintenance or social facilitation maintenance was significantly better than in the control group from randomization to post-weight maintenance treatment (behavioral skills maintenance: BMI z-score -0.04 , social facilitation maintenance: -0.04 , control: 0.05 , $p < 0.01$). Efficacy of the active maintenance treatment declined during the follow-up period, but remained significant in primary analysis when comparing BMI z-score outcomes from baseline to 2-year follow-up. Intention-to-treat analysis reduced the previously significant long-term treatment group vs. control group comparisons to non-significance. Child social problem scores moderated relative weight change from baseline to 2-year follow-up, with low social problem children in social facilitation maintenance having the best outcomes.

Conclusion(s): Short-term efficacy of weight loss treatment for children can be enhanced by addition of maintenance-targeted intervention. Declining effect sizes over follow-up strongly suggest the need for intensified maintenance strategies to sustain effects.

Effective prevention and treatment of childhood obesity are major public health challenges today. Practitioners in the field are confronted with high dropout rates and heterogeneous response rates [10], limited capabilities of mid- and long-term follow-up and often enough poor funding by health insurance companies. Not long ago, the authors of an excellent Cochrane review on interventions for

treating childhood obesity concluded that the quality of published data on childhood obesity interventions was too limited to draw generalizable conclusions and called for carefully designed, adequately powered randomized controlled intervention trials [11–14]. Since then, several research groups accepted this challenge and the results of their efforts began to be published only recently. The studies by Savoye et al., Golley et al. and Wilfley et al. are examples of well-designed intervention studies. All are randomized controlled trials (RCT) and their authors performed intention-to-treat (ITT) analysis on their outcome data. Furthermore, each study addresses a key issue in childhood obesity treatment, namely interventions in underprivileged minority children (Savoye et al.), parent-oriented interventions for younger children (Golley et al.), and strategies for effective weight maintenance after successful completion of a weight management program (Wilfley et al.).

Savoye et al. report the outcomes of a family-based lifestyle intervention with a special focus on the needs of inner city minority children (www.brightbodies.org). Given the study's setting, the described intensity of the program and the required commitment in time and effort of the participants, it is impressive to see that 71% of those in the intervention group completed the 12-month program. Participants in the intervention group achieved significant reductions in BMI and body fat mass after 6 months and these improvements were sustained at 12 months. Unfortunately, changes in BMI z-scores are not reported, so comparability to results from other studies is hampered. As could be expected, the intervention also improved cardiovascular risk factor profiles, especially the degree of insulin resistance was significantly lowered in the treatment group. As previous intervention studies have demonstrated, there may be thresholds in weight reduction that have to be reached in order to achieve significant improvements in cardiovascular risk in obese children.

Important for clinical practice

Effect of levothyroxine treatment on weight and body mass index in children with acquired hypothyroidism

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Background: It is well known that thyroid hormones play a key role in regulating basal metabolic rate. Hypothyroidism is associated with weight gain. Furthermore, it is known that obese children demonstrate moderately increased serum levels of TSH compared with children of normal weight [15]. This elevation of TSH is reversed during weight loss in obese children. So far only few data exist on the influence of thyroxine substitution in patients diagnosed with acquired hypothyroidism on body weight.

Methods: This study is a retrospective study involving 68 subjects with acquired hypothyroidism seen in the Division of Pediatric Endocrinology at the University Hospital in Lexington, Kentucky.

Results: Treatment with levothyroxine decreased the initially elevated TSH levels sufficiently. However, this was not associated with a significant change in weight or BMI. When the whole study group was divided into subgroups, patients of the group who lost weight had a mean initial TSH level which was significantly higher than that of the patients who showed no weight loss at the follow-up visit.

Conclusion(s): Most children treated for acquired hypothyroidism with levothyroxine exhibit little short-term changes in weight or BMI although a normalization of the TSH level has been achieved. However, patients with severe hypothyroidism and highly elevated TSH levels (mean level 349 $\mu\text{U/ml}$) show a small weight loss on follow-up. Practitioners should not expect significant decreases in body weight during treatment with levothyroxine in children with acquired hypothyroidism.

This study answers a question relevant to clinical practice. Interestingly the authors could not describe significant effects of levothyroxine substitution in patients with acquired hypothyroidism although their initial laboratory values clearly supported the diagnosis of acquired hypothyroidism. Only severe elevations of TSH have been associated with a small weight loss of 2.3 kg.

Most of the children in this study had significant biochemical hypothyroidism (84% had initial TSH levels $>10 \mu\text{U/ml}$, 59% had initial TSH levels $>20 \mu\text{U/ml}$).

The study has several limitations. It has been retrospective and included no age-matched control subjects. However, these data are relevant for practical work. They do not support the notion of hypothyroidism as a cause of obesity since also the overweight and obese patients in this cohort did not lose significant weight during treatment. Practitioners should be cautious in their expectation of weight loss after treatment in children with diagnosed hypothyroidism.

Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report

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Background: Childhood obesity is now recognized as a disease. There is a need for evidence-based treatment recommendations as well as for recommendations for a standardized assessment and prevention.

Methods: An Expert Committee comprised of representatives from 15 professional organizations, appointed experienced scientists and clinicians reviewed the literature.

Results: The expert group presents recommendations for approaches to prevent, assess and treat overweight and obesity in children and adolescents.

Conclusion(s): This updated review is helpful for practitioners working with obese children and adolescents and their families.

Recommendations for treatment of child and adolescent overweight and obesity

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Background: Childhood obesity is now recognized as a disease. There is a need for evidence-based treatment recommendations as well as for recommendations for a standardized assessment and prevention.

Methods: Current literature-based information about eating behaviors, physical activity behaviors and sedentary behaviors have been examined as well as studies of multidisciplinary behavior-based obesity treatment programs. Furthermore, information about more aggressive forms of treatment has been reviewed.

Results: The writing group of this article presents a comprehensive four-step approach for weight management that includes the following stages: (1) prevention plus, (2) structured weight management, (3) comprehensive multidisciplinary intervention, and (4) tertiary care intervention.

Conclusion(s): These updated recommendations are helpful for practitioners treating obese children and adolescents.

These two recommendations recognize the importance of social and environmental change to reduce the obesity epidemic but also identify ways healthcare providers and healthcare systems can be part of broader efforts. The Expert Committee recommendations revise the recommendations on childhood obesity published in 1998 [16]. The scarcity of studies about the process of obesity treatment resulted in recommendations which represent a consensus based on the best available information. In the review on recommendations for treatment of child and adolescent overweight and obesity, evidence has been reviewed about the treatment of obesity that may have applications in primary care, community, and tertiary care settings. The article does not only address specific patient behavior goals but also encourage practitioners to modify office systems to streamline office-based care and to prepare to coordinate with professionals and programs outside the office for more intensive interventions.

Both articles represent state-of-the-art recommendations which will be of great help for practical use in the assessment and treatment of children and adolescents with overweight and obesity by health-care providers and also institutions for pediatric endocrinology.

Reviews

Developmental origin of fat: tracking obesity to its source

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Background: The development of obesity not only depends on energy homeostasis in terms of food intake and caloric utilization, but is also dependent on the balance between white adipose tissue and brown adipose tissue. Different fat depots seem to have different metabolic and endocrine functions.

Results: This review summarizes the current literature on lineage determination of adipose cells, factors determining adipocyte differentiation, signals inducing adipose development, the heterogeneity of adipocytes among different white adipose tissue depots, developmental and patterning genes in white adipose tissue depots, potential heterogeneity within a single fat depot, specifying brown vs. white adipose lineages, factors controlling thermogenetic program of brown adipose tissue, and plasticity and regenerative capacity of adipose tissue.

Conclusion(s): The authors consider how the developmental origins of fat contribute to its physiological, cellular and molecular heterogeneity and explore how these factors may play a role in the growing epidemic of obesity.

The past two decades have shed considerable light on the role of factors controlling food intake and energy expenditure in body weight regulation [17] and on the transcriptional control and cell biology underlying conversion of preadipocytes to adipocytes [18–23]. Surprisingly little is known, however, about the developmental origin of adipose tissue, the control of brown vs. white preadipocyte commitment, the control of the relative amounts and functional heterogeneity among white fat cells in different depots, and the exact pathways and intermediates between the embryonic stem cell and the mature fat cell.

This review gives a new view on the adipose organ as a complex with multiple compartments composed of cells with different functions that most likely arise from different developmental lineages. It defines also open questions and research fields which seem important to deal with in the future.

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