Obesity and Weight Regulation

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We have been very happy to get 1,669 papers out of our established search strategy in PubMed which have been saved in our 2012 *Yearbook* EndNote database. We then selected 25 papers which in our mind have been the most exciting ones.

The highlights in this year's chapter are papers about longitudinal studies of body weight changes in children and new insights into the long-term risk of childhood obesity, reports about a larger group of patients with congenital leptin deficiency in Pakistan, several papers on remodeling of white adipose tissue and the biology of brown adipose tissue, and two exciting clinical studies published in the *New England Journal of Medicine*: Long-term persistence of hormonal adaptations to weight loss, and Neighborhoods, obesity, and diabetes – a randomized social experiment.

Thus, this *Yearbook* chapter on obesity and weight regulation covers again a broad research area ranging from genetics and epigenetics to human social environment.

Recent development in childhood obesity prevalence rates

Evidence that the prevalence of childhood overweight is plateauing: data from nine countries

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Background: Especially in developed countries, pediatric obesity has been described as the primary health problem in children. In the past 15 years increasing prevalence rates for overweight and obesity in children were reported in several states of the Western world as well as in developing countries. However, during the last few years several countries reported a slowing in the rise of childhood obesity, stagnation, or even a decline. This study assembles evidence from nine countries (Australia, China, England, France, Netherlands, New Zealand, Sweden, Switzerland, and USA).

Methods: Via literature alerts and personal contacts, authors who had recently published or presented plateauing data on childhood obesity were identified and asked to contribute to this paper. Other publications on prevalence data regarding childhood obesity have not been included. For cross-country comparison, data from all countries were compiled using the International Obesity Task Force (IOTF) cut-offs. With linear regression the yearly rate of change in the prevalence rates was calculated.

Results: With the exception of the French INCA1 study ($n = 1,017$ self-reported data), objectively measured weight and height data from 466,277 children aged 2–19 years could be analyzed. Between 1995 and 2008 a mean (SD) change of $+0.00$ (0.49)% in overweight and obesity prevalence rates across all age and sex groups and all countries could be calculated per year. Classified in overweight alone and obesity alone, the change was $+0.01$ (0.56)% and -0.01 (0.24)%, respectively. The authors could find differences in the rates of change according to sex, age, socioeconomic status and ethnicity.

This review article shows high-quality data concerning a plateauing of the rate of childhood overweight and obesity from nine countries. Analyzing 112 reports, the mean (SD) change in prevalence rates of overweight and obesity was $+0.00$ (0.49)% per year between 1995 and 2008. In 45% of the reports ($n = 50$) the authors found even declines. This leveling off in childhood obesity has also been

reported in Germany, Denmark, Scotland, Greece, Greenland and Russia [1–6]. Additionally, more recent data from the USA showed no further change in prevalence of obesity among US children and adolescents in 2009–2010 compared with 2007–2008 [7].

When comparing gender, the flattening was more marked for girls than for boys. Furthermore, the authors described age-related differences whereby declining prevalence rates were found more in preschool children (age 2–5 or 6) compared to primary school-aged children (6–11 or 12 years) or adolescents (12–19 years). Blüher et al. [8] could also show an age-specific stabilization in prevalence rates in German children with an upward trend for overweight and obesity prevalence rates in older children (8–16 years) compared to a downward trend in younger children (4–7.99 years).

There are a number of possible reasons for this declining trend. Factors in the social and physical environment probably play a role. One hypothesis is that these findings are the results of the cumulative effect of programs for preventing the development of childhood overweight and obesity, i.e. focusing on healthy eating and increased physical activity, initiated several years ago. In the last years, the awareness of this health problem has increased in healthcare professionals, schools, community organizations, industry, and governments which decreased environmental factors contributing to inappropriate weight gain. Another explanation is the saturation equilibrium hypothesis which says that overweight and obesity rates have reached a race- and/or country-specific ceiling. Despite the globally reported stabilization or decline, the prevalence rates of overweight and obesity in children remain on a high level and represent still a significant health issue. It is also not clear whether the reported stabilization represents a long-term change or is only a temporary finding. Because of this lack of clarity, this stagnating trend and possible causal factors should be further analyzed.

Food for thought

Progression from childhood overweight to adolescent obesity in a large contemporary cohort

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Background: Overweight during childhood is likely to persist or to progress to obesity in adolescence. This assumption is the basis for obesity prevention programs during childhood. However, there is only limited evidence for this assumption with respect to contemporary children.

Methods: Data from the Avon Longitudinal Study of Parents and Children (ALSPAC, children born in 1991 and 1992), which have been obtained longitudinally over a 6-year period, have been analyzed.

Results: The progression of overweight at the age of 7 years to obesity at the age of 13 years showed an adjusted odds ratio of 18.1 (95% CI 12.8–25.6). Approximately one third of the overweight children at age 7 were obese at age 13 years, one third in the healthy weight range at 13, and the remaining third remained overweight using definitions of overweight and obesity with UK BMI reference data.

Conclusions: This study quantifies the progression of overweight to obesity in a large contemporary cohort of children. The study provides a scientific basis to decide whether the overweight state might be a useful target for future obesity prevention programs. It supports recent expert committee guidelines stating that change in BMI should be monitored in children who are overweight.

Longitudinal study of body weight changes in children: who is gaining and who is losing weight?

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Obesity (Silver Spring) 2011;19:667–670

Background: Studies of temporal changes in obesity in general use a cross-sectional design to determine the prevalence of overweight and obesity at different time points. In several countries the well-known rise in the prevalence of childhood obesity has subsided. The aim of this study was to longitudinally assess the changes in body weight and body fat across a period of 28 months in a cohort of children who did not participate in a prevention trial and did not undergo extensive outcome assessment.

Methods: A total of 612 children in the 4th to 6th grades have been enrolled (10 schools, rural communities of Louisiana, USA). The follow-up investigation at month 28 could be performed in 74% of the children. Body fat was estimated by a body impedance analysis. The IOTF classification system was used to define overweight and obesity.

Results: Higher BMI percentile scores and percent body fat at baseline were associated with larger decreases in BMI and percent body fat after 28 months. Children with lower BMI percentiles at baseline tended to gain weight and children with higher BMI percentiles at baseline tended to lose weight. Similar findings were observed for changes in percent body fat. When these data were analyzed as cross-sectional studies, prevalence was found to be stable over the 28-month study period because incidence and remission rates were similar.

Conclusions: The results of this study suggest that children who are not overweight tend to gain weight whereas overweight children tend to lose weight as they grow older.

The effectiveness of childhood obesity prevention programs aimed at overweight children was highlighted in the most recent *Cochrane Review* [9]. There is however a yet insufficient evidence base of well-controlled studies with a meaningful long-term follow-up and there is a lack of studies providing an economic evaluation.

A recent systematic review concluded that overweight in childhood was likely to persist or to progress to obesity [10]. However, the evidence summarized in this review was limited in quantity, and was of limited generalizability to contemporary children. Most of the studies included children born before the 1980s.

On the one side, the study of Reilly et al. showed that the risk of obesity was 18–20 times higher for the overweight child at the age of 7 years compared with a normal weight child at the same age. However, on the other side, the absolute risk of obesity development for overweight children was lower than might have been expected (only one third).

The study of Williamson et al. shows that the prevalence of overweight and obesity might remain stable over time in cross-sectional studies although a significant number of normal weight children became overweight (incidence 13.1%) and a significant number of children became obese (incidence 4.3%). The differences in findings from longitudinal and cross-sectional perspectives illustrate how the two research designs can lead to very different conclusions and reinforce the utility of long-term research designs.

The results of both studies support recent expert committee guidelines [11–13] which strongly support that BMI should be monitored regularly in children over time. Longitudinal studies of weight changes in large nationally representative samples in a variety of countries are needed.

Childhood adiposity, adult adiposity, and cardiovascular risk factors

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N Engl J Med 2011;365:1876–1885

Background: There is accumulating evidence that cardiovascular risk factors associated with childhood obesity track into adulthood. Currently, the contribution of childhood overweight and obesity to cardiovascular risk in adulthood independent of adult BMI has not been clearly established.

Methods: Combined analysis of data from four prospective cohort studies (Bogalusa Heart Study, Muscatine Study (both USA), Childhood Determinants of Adult Health (Australia), and the Cardiovascular Risk in Young Finns Study (Finland) that measured childhood and adult BMI. For comparison of outcomes, study participants were categorized in four groups: group I included subjects with normal BMI in childhood and adulthood, group II consisted of subjects who were obese in childhood and nonobese as adults, group III those who were obese in childhood as well as in adulthood, and group IV entailed those who were normal weight in childhood and became obese in adulthood. Defined study outcomes were the presence of type 2 diabetes, hypertension, dyslipidemia, and increased intima media thickness (IMT).

Results: For analysis, data from 6,328 subjects with a mean length of follow-up of 23.1 ± 3.3 years were available. Subjects with persisting high BMI from childhood to adulthood (group III) and subjects who became obese as adults (group IV) had significantly elevated relative risks for type 2 diabetes (RR 5.4 (III), RR 4.5 (IV)), hypertension (RR 2.7 (III), RR 2.1 (IV)), high-risk LDL cholesterol (RR 1.8 (III), RR 1.5 (IV)), high-risk HDL cholesterol (RR 2.1 (III), RR 2.2 (IV)), high-risk triglycerides (RR 3.0 (III), RR 3.2 (IV)), and high-risk IMT (RR 1.7 (III), RR 1.5 (IV)) compared to subjects who had a consistently normal BMI (group I). The relative risks for adverse cardiovascular outcomes in subjects who were obese in childhood and nonobese in adulthood (group II) were comparable to the relative risks in group I.

Conclusions: Decreasing obesity between childhood and adulthood is associated with significant reductions in the relative risk for type 2 diabetes, hypertension, dyslipidemia, and increased intima media thickness in adulthood.

Adolescent BMI trajectory and risk of diabetes versus coronary disease

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Background: Obesity in adulthood is a major risk factor for the development of type 2 diabetes and coronary heart disease. The impact of BMI trajectory from adolescence to adulthood on obesity-related diseases remains to be elucidated.

Methods: This is a prospective study of 37,674 young men followed from the age of 17 years in regular intervals through the Staff Periodic Examination Center of the Israeli Army Medical Corps. Defined outcomes were the presence of type 2 diabetes, or the diagnosis of coronary heart disease defined as angiography-proven stenosis of more than 50% in at least one coronary artery.

Results: Data from study participants were available of a mean follow-up period of 17.4 ± 7.4 years, representing approximately 650,000 person-years. Adolescent BMI at age 17 predicted type 2 diabetes (hazard ratio 2.76, highest vs. lowest BMI decile) and coronary heart disease (hazard ratio 5.43, highest vs. lowest BMI decile) in midlife adjusted for age, blood pressure, sedentary behavior, smoking, family history and a range of biomarkers for cardiovascular risk. Further adjustment for the confounding effect of adult BMI removed the association of adolescent BMI with type 2 diabetes in adulthood (hazard ratio 1.01), but the increased risk for coronary heart disease still remained significant (hazard ratio 6.85). Furthermore, both BMI in adolescence and BMI in adulthood were independently associated with an increased risk for angiography-proven coronary heart disease.

Conclusions: The risk of coronary heart disease in midlife is associated with an elevated BMI in adolescence. This association holds true even for BMI levels in adolescence considered to be in the normal range.

Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review

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Int J Obes (Lond) 2011;35:891–898

Background: Over the last years a fair number of studies have been conducted examining the associations of obesity in childhood and adolescence with morbidity and premature mortality in adulthood. Lacking was a systematic review of the recent published evidence.

Methods: A systematic review of the literature was carried out comprising studies published between January 2002 and June 2010. Studies were eligible for inclusion in the review if they reported a measure of exposure to overweight or obesity in childhood or adolescence and data on morbidity or mortality as outcomes in adulthood. Studies reporting risk factors or surrogate markers of cardiovascular risk in adulthood were excluded.

Results: From an initial search result of 8,535 papers, 28 were identified reporting data on premature mortality in adulthood (8 papers), cardiovascular or metabolic comorbidities (11 papers), and other adverse outcomes (disability, cancer) associated with childhood obesity. Reported hazard ratios for premature mortality in adulthood ranged from 1.4 to 2.9. Only 1 of 8 studies did not find an increased adult mortality. Childhood obesity was uniformly associated with increased hazard ratios for the risk of diabetes, hypertension, coronary heart disease, and stroke (range 1.1–5.1) across 11 eligible studies. A further 9 studies were identified reporting a variety of outcome measures including increased cancer risk (5 studies), disability (2 studies), asthma and atopy (1 study), and polycystic ovary syndrome (1 study) in adulthood.

Conclusions: Recently published evidence demonstrates a substantial adverse impact of overweight and obesity in childhood and adolescence on long-term morbidity and mortality.

The obesity epidemic has now been a major concern for healthcare service providers and policymakers for almost two decades. Often driven by vast media coverage, the threat of childhood obesity to our healthcare systems has been a major focus of the public perception. Remarkably, the interaction of BMI in childhood and adolescence and BMI in adulthood on the risk of future disease has not been well established. In 2011, two landmark studies published in the *New England Journal of Medicine* by Juonala et al. and Tirosh et al. now further our knowledge on the differential impact of childhood versus adult obesity on established cardiovascular risk factors and cardiovascular endpoints.

First, in a pooled analysis of the datasets of four seminal cohort studies, Juonala et al. find a markedly increased cardiovascular risk associated with childhood overweight and obesity. Except for high-risk triglycerides, subjects with a consistently elevated BMI from childhood to adulthood had the most pronounced risk for adverse cardiovascular outcomes, closely followed by those who had a normal BMI during childhood and became obese as adults. However, the most important result of this analysis is the finding of a complete attenuation of the excess cardiometabolic risk by normalization of weight status between childhood and adulthood.

Second, investigating an impressively large database of the Israeli Armed Forces, Tirosh et al. demonstrate that the risk of type 2 diabetes in adulthood depends mainly on adult BMI but not on adolescent BMI. Contrasting this finding, and warranting interesting insight into the age- and time-dependent evolution of different pathophysiological routes to cardiovascular disease, the same study found independent associations of adolescent BMI and adult BMI with angiography-proven coronary heart disease (CHD). In fact, adjusted for a wide array of potential confounders including adult BMI, the risk for clinical CHD in adulthood was elevated sevenfold for adolescents in the highest BMI decile compared to adolescents in the lowest BMI decile. The average BMI trajectories between ages 17 and 45 years for subjects later affected by diabetes or coronary heart disease ranged between the 50th and 75th percentiles of the entire cohort. These results underscore the importance of BMI for the long-term health consequences and will surely refuel the ongoing debate on 'healthy' BMI ranges.

Third, and completing the picture, Reilly and Kelly provide a comprehensive review of recently published studies on this topic. Compared to the last systematic review in 2003 [14], which only found convincing evidence for the tracking of obesity from childhood into adulthood, the authors now present a considerable body of evidence on the relationships between childhood obesity and morbidity and mortality in later life. Childhood obesity was associated with consistently elevated risks for premature mortality, type 2 diabetes, hypertension, coronary heart disease, stroke, polycystic ovary syndrome, cancer (especially breast cancer), and atopy.

Programming and epigenetics

Epigenetic gene promoter methylation at birth is associated with child's later adiposity

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Background: Genome-wide association studies suggest that fixed genetic variation makes a relatively small contribution to the risk for obesity development. Animal studies as well as epidemiological data provide evidence that perinatal factors have an important influence on obesity development possibly due to epigenetic changes.

Methods: The methylation status of CpGs in the promoters of candidate genes in DNA extracted from umbilical cord tissue obtained at birth was analyzed using Sequenom MassARRAY.

Results: In cohort 1, retinoid X receptor- α (RXRA) chr9: 136355885+ and endothelial nitric oxide synthase (eNOS) chr7: 150315553+ methylation were independently positively associated with gender-adjusted childhood fat mass at the age of 9 years (measured by DEXA), and explained >25% of the variance in childhood adiposity. Higher methylation of RXRA chr9: 136355885+ was associated with lower maternal carbohydrate intake in early pregnancy. The association between fat mass and methylation status was confirmed for RXRA chr9: 136355885+ in a second cohort.

Conclusions: This study provides novel evidence for the importance of the developmental contribution to the growth of body fat mass. The methylation status of RXRA chr9: 136355885+ measured at birth seems to have a strong influence on fat mass development in later childhood.

These are exciting results in humans showing that the epigenetic gene promoter methylation at birth influences the development of body fat mass during childhood. Evidence for perinatal factors in programming metabolism and also body fat mass development during later life has been established in animal studies and was previously only suggested for humans on the basis of epidemiological findings, e.g. famine during pregnancy is associated with obesity in adult offspring [15]. Epigenetic processes such as DNA methylation and histone modifications allow environmental factors to modulate gene transcription. Many of these changes are then stable throughout the life course [16]. Although epigenetic processes operating in perinatal life have been implicated in the origins of obesity, there is yet no direct evidence for this proposition in humans.

The results of this study also indicate a potential mechanistic pathway involved, because induction of transcription by RXRA is dependent on its binding to ligands including the peroxisome proliferator-activated receptors involved in insulin sensitivity, adipogenesis, and fat metabolism.

The findings of this study raise the possibility that the developmental environment and the resulting epigenetic changes may be equally or even more important than germline genetic variations in their contribution to the risk of obesity.

Leptin deficiency and leptin gene mutations in obese children from Pakistan

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Int J Pediatr Obes 2011;6:419–427

Background: Congenital leptin deficiency is an extremely rare monogenetic cause for infant obesity. Nearly half of the known patients have a Pakistani background and carry the same homozygous mutation Δ G133 in the leptin gene.

Methods: A cohort of 25 extremely obese Pakistani children was screened for leptin levels. In all patients with low levels of leptin, leptin gene sequencing was performed.

Results: Low or undetectable leptin levels were found in 9 children. Seven were homozygous for the Δ G133 mutation. The other 2 children carried novel homozygous mutations (c.481_482delCT and c.104_106delTCA).

Conclusion: The Δ G133 mutation appears to be a founder mutation in Pakistan.

High prevalence of leptin and melanocortin-4 receptor gene mutations in children with severe obesity from Pakistani consanguineous families

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Mol Genet Metab 2012;106:121–126

Background: Since Pakistan has a very high rate of consanguinity, a significantly higher incidence of monogenic obesity is expected in this population.

Methods: 62 unrelated obese Pakistani children of consanguineous parents were screened for mutations in the coding regions of the leptin gene (LEP) and the melanocortin-4 receptor (MC4R) gene

Results: LEP mutations were found in 16.1% of the children. Of these, 9 children were homozygous for the Δ G133 mutation, and 1 child had a novel homozygous mutation involving a deletion of 3 base pairs (I35del). In addition, homozygous MC4R mutations, M161T and I316S, were identified in 2 subjects.

Conclusion: In this consanguineous population, up to 20% of childhood obesity is caused by monogenetic forms of obesity.

These two and the following article by Niard et al. all have in common that they challenge our current beliefs on leptin. The adipocyte-derived hormone leptin is one of the key factors regulating weight both in mammals and in human beings. Apart from gross obesity mainly due to hyperphagia, leptin deficiency and resistance also lead to a number of neuroendocrine and metabolic changes.

Before the two articles above were published, only 15 patients with leptin deficiency had been identified worldwide [17–25]. Since nearly half of these patients have a Pakistani background and carry the Δ G133 mutation, it has been suggested that this might be a founder mutation in Pakistan. Both the articles by Fatima et al. and Saeed et al. prove this assumption to be right. Still it is surprising that within their fairly small samples they found such a high number of affected children (28 and 15% respectively). Even more astonishing though is the fact that each group discovered new homozygous leptin gene mutations. For the two mutations found by Fatima et al., it still has to be proven that they are functionally relevant. Both affected children were morbidly obese and had low leptin levels, but as they were only 7 and 18 months old at the time of the screening, their low leptin levels might still be physiological. However, if all three novel gene changes are true mutations we have to ask ourselves why there is such a high number of leptin gene mutations in Pakistan since, despite massive research efforts, no others have been found in other regions of the world, even within consanguineous populations [26]. It is tempting to speculate that the heterozygous state might confer some advantage in a region with recurrent food shortages.

Pregnancy in a woman with a leptin-receptor mutation

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N Engl J Med 2012;366:1064–1065

Background: Human leptin deficiency and resistance have been shown to lead to a severely delayed puberty with irregular menses in women. So far, no pregnancy has been reported in patients with these rare diseases.

Case Report: A patient with a homozygous leptin receptor gene mutation and morbid obesity showed a delayed puberty with irregular cycles after the age of 17 years. A gastric bypass was performed at 24 years of age, leading to a BMI decrease from 81 to 62 kg/m².

Results: Two years after gastric bypass the patient became pregnant. After a normal pregnancy she delivered a healthy normal weight son in the 38th gestational week.

Conclusion: Apparently, in humans leptin function is not essential for reproduction.

The most profound neuroendocrine disturbance in mice with homozygous mutations in the leptin receptor gene (*db/db* mice) or in the leptin gene (*ob/ob* mice) [27] is infertility. Until now, it was also assumed that without leptin action humans are not able to reproduce. This described pregnancy in a woman with a homozygous leptin receptor mutation therefore challenges our current knowledge on leptin action. Three possible explanations can be postulated for this unexpected event.

The first explanation for the patient's fertility might be her weight loss. Here we find a connection to the mouse model since male (but not female) *ob/ob* mice become fertile if kept on a severely restricted diet [28]. Another explanation is more complex yet very interesting. There is some evidence that the main effect of leptin is on the timing of maturation of the hypothalamic-pituitary-gonadal axis, rather than on its subsequent function. Patients with leptin deficiency or resistance show hypogonadotropic hypogonadism during adolescence [25, 26, 29], which normalizes rapidly under leptin substitution in those with leptin deficiency [30]. However, even without leptin substitution, patients with leptin deficiency or leptin resistance develop a spontaneous if severely delayed puberty and show normal LH/FSH secretion in adulthood [21, 26, 29]. That a woman with leptin receptor deficiency can become pregnant is consistent with this overall picture.

Leptin has no direct effect on gonadotropin-releasing hormone (GnRh) neurons since those do not express leptin receptors. Therefore other factors must translate the impact of leptin on GnRH secretion. Immediate downstream mediators of leptin include α -MSH and agouti-related peptide. Leptin increases α -MSH secretion, which stimulates MC4R and lowers agouti-related peptide secretion which inhibits MC4R. Leptin deficiency or resistance leads to an inhibition of MC4R because agouti-related peptide rises. Two very recent studies in *db/db* [31] and *ob/ob* [32] mice showed that ablation of agouti-related protein [31, 32] or heterozygosity of MC4R [31] restores fertility in these mice. Ablation of agouti-related peptide reverses the MC4R inhibition triggered by leptin deficiency or resistance. Also, heterozygosity of MC4R reduces the influence of an inhibited MC4R. Since homozygous or heterozygous MC4R mutations do not lead to changes in pubertal development or fertility either in mice or in humans, MC4R cannot confer a permissive effect of leptin on pubertal development. However, the experiments show that inhibition of MC4R due to leptin deficiency inhibits pubertal development and fertility and an ablation of this inhibition restores fertility. Therefore, a heterozygous MC4R mutation in the above-described patient could also explain the unexpected pregnancy.

Leptin modulated changes in adipose tissue protein expression in *ob/ob* mice

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Obesity 2011;19:255–261

Background: The satiety hormone leptin is produced from adipocytes. It exerts its functions in the central nervous systems regulating food intake and energy expenditure. Leptin-deficient *ob/ob* mice rapidly lose their body fat upon treatment with recombinant leptin. This effect is mainly due to a decrease in food intake. There is increasing evidence that the loss of adipose tissue is also mediated at least in part by apoptosis of fat cells. The aim of this study was to elucidate how subcutaneous infusion of leptin changes the expression profile of adipose tissue in *ob/ob* mice in order to learn how peripheral actions of the hormone might contribute to weight loss.

Methods: Leptin was administered to *ob/ob* mice by osmotic minipumps (0 vs. 10 µg/day for 14 days). Adipose tissues were subjected to two-dimensional gel electrophoresis, MALDI-TOF MS and real-time RT-PCR.

Results: Leptin-treated mice had significantly lower fat pad weights compared to vehicle-treated control animals. Twelve protein groups were differentially expressed in adipose tissues in both groups including chaperones and redox proteins (e.g. calreticulin, prohibitin, peroxiredoxin-6), and cytoskeleton proteins (β-actin, desmin, α-tubulin). These findings were confirmed on the mRNA level.

Conclusions: The authors conclude that the effects of leptin on adipose tissue might be mediated by changes in expression on chaperones and redox proteins, which regulate endoplasmatic reticulum stress, and cytoskeletal proteins, which regulate mitochondrial morphology.

Patients with congenital leptin deficiency suffer from morbid obesity resulting from severe hyperphagia. Upon treatment with recombinant leptin, their body weight decreases and adipose tissue depots rapidly shrink. Suppression of hyperphagia and normalization of food intake via central nervous mechanisms are mainly responsible for the weight loss, but also increased energy expenditure might play a role here. In *ob/ob* mice leptin treatment led to an increase of lipid mobilization and white adipocytes seem to be converted into lipid-oxidizing cells. Most interestingly, the rapid loss of fat mass led was mediated by apoptosis of fat cells, once more demonstrated in this study.

The important finding of this study is that treatment with leptin targets the expression profile of adipose tissue. However, whether leptin is directly acting on adipocytes, whether its effects are mediated via the central nervous system, or whether its effects are secondary to weight loss remain unanswered.

Remodeling of white adipose tissue

Adipose tissue remodeling in children: the link between collagen deposition and age-related adipocyte growth

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Background: Remodeling of the extracellular matrix (ECM) is important for adipose tissue growth and expansion. The aim of this study was to investigate if ECM remodeling plays a role in adipose tissue of healthy, growing children.

Methods: Subcutaneous adipose tissue biopsies were taken from 65 healthy children. Immunohistochemistry and qPCR was performed to study collagen, macrophages and T cells.

Results: Normal weight children had significantly more total collagen than overweight children. Adipocyte size was negatively correlated with total and pericellular collagen, but positively correlated with the percentage of macrophages. The percentage of total collagen was inversely associated with BMI Z-score and age. Older children (>11 years) in the top BMI Z tertile had less collagen (3.8%) than younger (2–5 years) children in the bottom BMI Z tertile (12.6%). There was no evidence of crown-like structures or T-cell infiltration into adipose tissue in children.

Conclusions: Increased collagen in adipose tissue is associated with decreased fat cell size and BMI Z-score and increased anti-inflammatory M2 macrophages in healthy, growing children. This suggests a dynamic interaction between immune cells and ECM remodeling even at an early age.

Subcutaneous adipose tissue remodeling during the initial phase of weight gain induced by overfeeding in humans

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J Clin Endocrinol Metab 2012;97:E183–192

Background: Adipose tissue remodeling plays an important role during weight gain. The aim of this study was to elucidate molecular pathways involved in adipose tissue remodeling during the initial phase of weight gain.

Methods: 44 healthy men received a lipid-enriched diet (+760 kcal/day) for 2 months. Subcutaneous abdominal adipose tissue biopsies were taken and subjected to histology and transcriptomics at baseline, after 2 weeks and after 2 months.

Results: Significant weight gain occurred on overfeeding. Gene expression patterns in adipose tissue were altered with an upregulation of genes related to lipid metabolism and storage, angiogenesis and matrix remodeling. There was increased microvascular density and connective tissue deposition, but no change in adipose tissue inflammation. Induction of the renin-angiotensin system as well as inhibition of Wnt pathway might be implicated in the observed remodeling processes.

Conclusions: Molecular changes during the early phase of weight gain in humans were identified. The identified pathways might provide potential targets for the treatment of pathological adipose tissue development as seen in obesity.

Adipose tissue represents the major store for energy in the body and as such has an almost unlimited capacity to expand. The cellular response to changes in energy intake involves tightly coordinated remodeling processes.

The paper of Tam et al. demonstrates that remodeling of the extracellular matrix occurs during growth and expansion of healthy children. Several animal models of genetic and diet-induced obesity have demonstrated that increasing fat mass leads to an acceleration of remodeling and subsequently to development of fibrosis. Alligier et al. performed a clinical study in humans to elucidate if diet-induced obesity in fact induces adipose tissue remodeling and fibrosis in humans. As expected, genes involved in ECM remodeling, angiogenesis, inflammation and lipid metabolism were most prominently altered. These pathways and genes represent promising targets to correct the fibrotic/inflammatory orchestration of remodeling processes in obesity.

A PGC1- α -dependent myokine that drives brown-fat-like development of white fat and thermogenesis

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Introduction: PGC1- α is a transcriptional coactivator which drives many biological pathways related to energy metabolism. Originally described as a modulator of uncoupling protein 1 (UCP-1) expression in brown adipocytes, it has been shown to stimulate mitochondrial biogenesis, angiogenesis and fiber-type switching in exercised muscle. Transgenic mice overexpressing PGC1- α in muscle are resistant to age-related obesity, suggesting the presence of a muscle-secreted factor which affects other tissues.

Methods: The authors used a transgenic mouse model overexpressing PGC1- α in skeletal muscle to investigate PGC1- α effects on energy metabolism and brown adipose tissue recruitment.

Results: Enhanced expression of PGC1- α in muscle stimulates an increase in expression of FNDC5, a membrane protein that is cleaved and secreted as a newly identified hormone, termed irisin. Irisin induces UCP-1 expression and a broad program of brown-fat-like development in white adipocytes *in vitro*. Furthermore, it is induced with exercise in mice and humans, and the authors could show that mildly increased irisin levels in the blood cause an increase in energy expenditure in mice with no changes in movement or food intake.

Conclusion: The authors conclude that irisin could be therapeutic for human metabolic disease and other disorders that are improved with exercise.

Brown adipose tissue is present and active in adult humans and first evidence has shown that this tissue is involved in cold-induced non-shivering thermogenesis in the human body [33]. In this study, Boström et al. discovered a novel hormone which acts as a chemical messenger between muscle and adipose tissue and has significant impact on brown fat recruitment and energy metabolism. This study elegantly demonstrates the impact of physical exercise on the recruitment of brown adipocytes.

The work group of Paul Spiegelman identified a novel myokine called ‘irisin’ during a search for genes regulated by PGC1- α . After physical exercise, it is secreted from the muscle into the bloodstream by proteolytic cleavage of its precursor FNDC5 – a type I membrane protein. When irisin levels rise, the hormone acts directly on white adipose tissue by inducing the formation of brown adipocytes. When administered during adipogenic differentiation of primary preadipocytes, FNDC5 induced key molecules of brown adipocytes *in vitro*. This was accompanied by an increase in oxygen consumption. Overexpression of FNDC5 in mice leads to enhanced irisin plasma levels and the formation of brown adipocyte islets in white adipose tissue. Along with the induction of brown fat recruitment, irisin improved glucose tolerance and reduced fasting insulin in mice fed a high-fat diet.

This discovery might be a first step in understanding the biological mechanisms that translate physical exercise into beneficial changes throughout the body, both in healthy people and in preventing or treating obesity and type 2 diabetes mellitus. This definitely will lead to further attempts to develop strategies to use irisin as an antiobesity drug.

Pediatric brown adipose tissue: detection, epidemiology, and differences from adults

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Introduction: Previous histological studies have suggested that brown adipose tissue (BAT) peaks in childhood and declines into adulthood. However, recent studies using PET-CT revealed the existence of active brown fat even in adults with a characteristic anatomical distribution. Moreover, a strong negative correlation between BMI and BAT activity has been shown. The objective of this study was to evaluate the prevalence and factors affecting the detection of active brown adipose tissue (BAT) in children and adolescents using ^{18}F -fluorodeoxyglucose positron emission tomography.

Methods: A retrospective review of 385 PET-CT scans for different oncologic indications of 172 patients aged 5–21 years was performed. BAT activity in the neck, thorax, and abdomen was compared to liver values. Clinical indices were recorded.

Results: There was no significant difference between prevalence of BAT activity in girls vs. boys and highest activities were found in cervical-supraclavicular regions. The highest percentage of patients with detectable BAT and the highest BAT/liver activity were in the 13- to 14.99-year age group in both males and females. BMI percentile correlated negatively with BAT activity, while BAT activity did not show any correlation with outdoor temperature and diagnosis.

Conclusion: BAT is detected more frequently in children than in adults under clinical, temperature uncontrolled conditions. BAT activity correlated inversely with obesity, suggesting that BAT plays a fundamental role in pediatric metabolism.

Despite the relative high number of studies investigating the relationship of BAT and factors which affect its activity status, little was known regarding the demographics of active BAT in children and adolescents.

In this study, 385 scans of pediatric patients undergoing PET-CT for cancer surveillance were investigated. In contrast to adults, there was no sexual dimorphism. BAT activity was negatively correlated with BMI. Interestingly, BAT appearance and BAT/liver activity was highest in the 13- to 14.99-year group, pointing to a potential important role of BAT on metabolism at the time of the adolescent growth spurt. That is even more striking, since it was the dogma for a long time that BAT appearance peaks after birth and declines subsequently afterwards.

This study shows for the first time that BAT activity peaks in adolescents and that BAT activity negatively correlates with BMI in children. However, these data were acquired without controlling for body temperature. As admitted by the authors, this might interfere with measures of active BAT.

Functional brown adipose tissue is related to muscle volume in children and adolescents

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Introduction: It has been suggested in PET-CT studies that brown adipose tissue (BAT) activity is correlated with anthropometric measures in adults. The aim of this study was to test if BAT activity correlated with anthropometric parameters in children.

Methods: Regression analyses were performed in 71 pediatric patients with or without BAT activity in PET/CT scans to assess the relation between BAT and body mass, obesity and musculature.

Results: 30 patients had detectable BAT in PET-CT scans (10 girls and 20 boys). There were no differences in age, BMI and subcutaneous fat mass between the groups. However, patients with BAT had significantly greater neck and gluteus musculature. With logistic regression analyses, neck and pelvic musculature predicted the presence of BAT independently of age, sex, body size, and season of scan.

Conclusion: The authors conclude that pediatric patients with visualized BAT on PET/CT examinations have significantly greater muscle volume than patients with no visualized BAT.

Unlike white adipocytes, brown adipocytes and myocytes share the same progenitor cell originating from the paraxial mesoderm. Moreover, brown adipocyte progenitors have been found in muscle. In the present study, the correlation between BAT appearance in PET/CT scans with BMI, age and skeletal muscle volume was investigated. Interestingly, they found a correlation between visualized BAT and muscle volume underlining the potential relationship between muscle and BAT development. However, one has to be careful about drawing such conclusions from retrospective PET-CT scans, as the patients were not scanned under controlled temperature conditions. Moreover, it has been shown that PET-CT is not sensitive enough to detect small amounts of BAT [34].

Retinaldehyde dehydrogenase-1 regulates a thermogenic program in white adipose tissue

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Introduction: Brown adipose tissue (BAT) may be involved in body weight regulation and recruitment of BAT may prevent obesity. Recent data link retinoids to energy balance, but a specific role for retinoid metabolism in white versus brown fat is unknown. Rate-limiting enzymes in retinol metabolism are retinaldehyde dehydrogenases (Aldhs).

Methods: The authors used an Aldh1a1 knockout mice to investigate the impact of retinol metabolism on energy metabolism and BAT recruitment.

Results: Aldh1a1 is predominately expressed in white adipose tissue (WAT). Deficiency of the Aldh1a1 gene induced genes characteristic for BAT leading to uncoupled mitochondrial respiration and adaptive thermogenesis. WAT-selective Aldh1a1 knockdown resulted in reduced weight gain and improved glucose homeostasis in mice. Rald induced uncoupling protein-1 (Ucp1) mRNA and protein levels in white adipocytes by selectively activating the retinoic acid receptor (RAR), recruiting the coactivator PGC-1 α and inducing Ucp1 promoter activity

Conclusion: Aldh1a1 and its substrate Rald are regulators of thermogenesis in white adipocytes. These findings may have potential therapeutic implications.

Metabolites of vitamin A – retinoids – have been linked to diverse biological functions including adipogenesis and energy homeostasis. The rate-limiting step of retinol metabolism is the conversion of retinaldehyde (Rald) to retinoic acids by aldehyde dehydrogenases (Aldh). This study nicely shows the impact of Rald on brown adipocyte formation in white adipose tissue.

First, the authors found a high expression of Aldh1a1 in mouse WAT compared to BAT. Moreover, the expression of this enzyme was found to be increased in obese humans and in mice on a high-fat diet, pointing to its role in regulating fat mass. They further investigated the phenotype of Aldh1a1^{-/-} mice. Interestingly, these animals had higher energy expenditure and body temperature compared to wild-type mice, which was accompanied by the formation of brown adipocytes in visceral adipose tissue. The authors then further investigated this effect on white adipocyte in vitro. Treating the cells with either Rald or with antisense oligonucleotides directed against Aldh1a1 induced brown adipocyte marker genes in white adipocytes. Moreover, Rald treatment induced the recruitment of PGC1- α via a RAR-dependent mechanism and induced UCP-1 promoter activation.

Dissipating energy stores by promoting thermogenesis in WAT has been proposed to be an approach to combat overweight and obesity. Disruption of Aldh1a1 in white adipose tissue might lead to new therapeutic strategies in obesity treatment.

Orexin is required for brown adipose tissue development, differentiation, and function

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Cell Metab 2011;14:478–490

Background: Orexin (OX) neuropeptides play a role in regulating food intake and wakefulness. Deficiency of orexin has been linked to narcolepsy, a disease which is associated with obesity.

Methods: Orexin-deficient mice were metabolically characterized. The effect of orexin-A on brown adipose tissue (BAT) development was investigated.

Results: Obesity in orexin knockout mice is associated with impaired BAT thermogenesis due to a defect in differentiation of brown adipocyte precursor cells. This defect was circumvented by orexin injection to orexin-null dams. In vitro, orexin was able to induce the full differentiation program into brown adipocytes of mesenchymal progenitor stem cells, embryonic fibroblasts and brown preadipocytes dependent on p38, bone morphogenetic protein receptor-1a (BMPR1A) and Smad 1/5 signaling.

Conclusion: The authors conclude that orexin plays an important role in brown adipose tissue differentiation and function with effects on adaptive thermogenesis and body weight regulation.

Several transcription factors which promote brown adipocyte differentiation have been identified. However, much less is known about factors which initiate these transcriptional events. In this study, Sellayah et al. provide surprising data connecting orexin neuropeptides with brown adipocyte formation.

Orexins are neuropeptides which regulate wakefulness and also food intake. Interestingly, they have been mentioned also in context of obesity. The authors found that orexin knockout mice became obese while eating less compared to wild-type animals. They showed also that this effect was due to an increased metabolic efficiency, which led them to investigate brown adipose tissue plasticity in these animals. In orexin-deficient mice, BAT was delipidated which was accompanied by reduction in the expression of brown adipocyte marker genes. In an elegant experiment, this effect could be circumvented in the offspring of orexin-null dams by injecting orexin in the dams during pregnancy. Interestingly, the effects of orexin on BAT development are mediated directly, as shown in in vitro experiments using mouse embryonic stem cells or primary brown preadipocytes.

This study provides evidence that orexin plays a significant role in the development of brown adipose tissue. Investigating the signaling pathways activated by orexin might lead to new and promising strategies to develop therapies against obesity and its related comorbidities.

New mechanisms

Dysfunction of lipid sensor GPR120 leads to obesity in both mouse and human

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Nature 2012;483:350–354

Background: Free fatty acids (FFA) serve as important energy source and signaling molecules at the same time. Several G-protein-coupled receptors for FFA have been identified so far, among them GPR120.

GPR120 is a receptor for unsaturated long-chain FA and is not only important for regulation of appetite and food preference, but also adipogenesis.

Methods: GPR120 knockout mice were generated and metabolically characterized. ~7,000 obese patients and ~7,000 controls were genotyped for variants in the GPR120 gene.

Results: GPR120-deficient mice develop obesity, glucose intolerance and fatty liver on a high-fat diet. Adipocyte differentiation and lipogenesis were impaired in these mice, while hepatic lipogenesis was enhanced. Mice were characterized by insulin resistance with reduced insulin signaling and increased adipose tissue inflammation. The expression of GPR120 in adipose tissue was significantly higher in obese humans compared to lean controls. A deleterious non-synonymous mutation (p.R270H), which inhibited GPR120 signaling, was discovered by exon sequencing. This variant was associated with increased obesity risk in Europeans.

Conclusions: The authors demonstrate that GPR120 is an important lipid sensor, which plays an important role in controlling energy balance in both humans and rodents.

GPR120 is highly abundant in the digestive tract. When food enters the gut, fatty acids bind to and activate GPR120 leading to secretion of gastrointestinal peptides such as cholecystokinin, glucagon-like peptide-1 and peptide YY. This informs the central nervous system about the availability of fatty acids and allows an adaptive response. Therefore, activation of GPR120 is one of the first steps in sending a satiety signal from the periphery to the brain.

The study from Ichimura et al. underlines the importance of GPR120 for the development of overweight and obesity. Mice deficient in GPR120 are more prone to diet-induced obesity and hepatic steatosis. Certain mutations in the GPR120 gene, which lead to inactivation of the receptor, seem to increase a person's risk of obesity by 60%.

Modulating the function of receptors involved in nutrient signaling, among them GPR120, might be a new pharmacological option for the treatment of obesity and its comorbidities.

Food for thought

Long-term persistence of hormonal adaptations to weight loss

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Background: Weight loss alters the circulating levels of several peripheral hormones involved in body weight regulation and increases subjective appetite. Whether these changes are transient or persistent over time will further the understanding of the widely observed challenges in maintaining the lowered body weight.

Methods: 50 overweight and obese subjects were enrolled in an 8-week weight loss program, followed by a 1-year weight maintenance period. Circulating levels of leptin, ghrelin, peptide YY (pYY), gastric inhibitory polypeptide (GIP), glucagon-like peptide 1 (GLP-1), amylin, pancreatic polypeptide (PP), cholecystokinin (CCK), and insulin were measured along with subjective ratings of hunger proxies at baseline, 2 weeks, and 1 year after completion of the weight loss period. At each time point, samples were obtained before and 30, 60, 120, 180 and 240 min after a standardized breakfast to shed light on changes in fasting values as well as modifications in postprandial hormone excursions.

Results: 36 subjects completed the study and were included in the analyses. Subjects lost 13.5 ± 0.5 kg (SE) on average, weight after 1 year remained 7.9 ± 1.1 kg below baseline. Weight loss produced significant reductions in leptin ($p < 0.001$), leptin/fat mass ($p < 0.001$), pYY ($p < 0.001$), CCK ($p < 0.001$), insulin ($p < 0.001$), and amylin ($p = 0.002$), and increases in ghrelin ($p < 0.001$), GIP ($p = 0.004$), PP ($p = 0.008$), and subjective appetite ($p < 0.001$). One year after the initial weight loss, these changes persisted for leptin ($p < 0.001$), pYY ($p < 0.001$), CCK ($p = 0.04$), insulin ($p = 0.01$), ghrelin ($p < 0.001$), GIP ($p < 0.001$), PP ($p = 0.002$), and subjective hunger ($p < 0.001$).

Conclusions: The authors conclude that weight loss-induced changes in peripheral hormones persist after 1 year. Thereby, they may contribute to the observed propensity to regain weight, and long-term strategies to counteract these changes may prevent obesity relapse.

It is known from previous studies that leptin, an adipocyte hormone, acts in the hypothalamus to reduce food intake and increase energy expenditure. The gastrointestinal hormones PYY, GLP-1, CCK, PP and amylin are released postprandially and inhibit hunger and further food intake [35–39]. To an opposite effect, ghrelin stimulates hunger [40] and GIP promotes energy storage [41, 42]. Thus, the hormonal changes found in this study can be expected to promote increased food intake, and thereby contribute to weight gain. This is substantiated by the reported increase in hunger and appetite ratings.

However, no comparison was made with a BMI-matched control group that did not undergo weight loss. Thus, some of the reported changes might be physiological at the lower BMI. Analogous to the reduction in insulin levels that go along with increased insulin sensitivity, as illustrated by the HOMA-IR reported in the supplemental materials, other hormonal alterations might be an effect of altered end-organ sensitivity and have no immediate consequences on intake regulation.

Despite these limitations, the study sheds light on possible physiological factors that contribute to the widely observed rebound phenomenon after weight reduction diets, and will certainly inform further investigations to clarify the underlying mechanisms.

Clinical review

Regulation of food intake, energy balance, and body fat mass: implications for the pathogenesis and treatment of obesity

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J Clin Endocrinol Metab 2012;97:745–755

Background: Although substantial progress has identified neurohumoral mechanisms underlying obesity, current nonsurgical treatment approaches are insufficient to help most obese individuals in achieving and maintaining a meaningful reduction in body weight. This review provides a synthesis of research articles providing insight into the mechanisms controlling food intake in the context of energy homeostasis with a focus on obesity pathogenesis, the dramatic recent increase in obesity prevalence, and the insufficient effectiveness of current nonsurgical treatment programs.

Methods: Research articles with highest quality evidence were included in the review.

Results: The authors summarized research findings in a structured way under six headlines: short-term, meal-related determinants of food intake, long-term regulation of food intake and energy balance, food reward and palatability, obesity and energy homeostasis, genetic factors, and leptin resistance: cause or effect of obesity? Interventions that reduce body fat stores elicit compensatory responses that promote the recovery of lost fat and are difficult to consciously override. Obesity involves the biological defense of an elevated level of body fat.

Conclusion: Essential breakthroughs are needed in understanding the biological defense of elevated body fat mass required to enable the development of effective new obesity prevention and treatment strategies.

This clinical review summarizes the current scientific knowledge about the regulation of food intake, energy balance, and body fat mass in a comprehensive manner. It explains why obesity is resistant to effective, long-term treatment when classical non-surgical approaches are applied. Body fat stores are subject to homeostatic regulation in obese individuals, just as in lean individuals. We are still waiting for essential breakthroughs in understanding the biological mechanisms that 'defend' against any reductions in our high levels of body fat mass.

Ghrelin levels increase after pictures showing food

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Background: The neuropeptide ghrelin is mainly secreted by the stomach and small intestine. It represents a potent orexigenic stimulus, as it increases self-rated appetite, caloric intake, and the propensity to initiate a meal. Ghrelin levels physiologically increase before meals, but to date the interplay of intrinsic and external factors that modulate this rise is incompletely understood. If external factors such as visual food cues play a role, this might be one of the mechanisms through which environmental factors potentiate obesity risk.

Methods: The influence of viewing pictures of food on circulating levels of ghrelin, leptin and insulin was assessed in comparison to neutral pictures with non-food contents. In two sessions, food vs. non-food pictures were shown to 8 healthy male volunteers in a cross-over design. Subjects were provided a standard breakfast at 08:00 h and lunch at 12:00 h. 50 pictures were repeatedly presented for 30 min starting at 10:30 h. Pictures displayed food contents during the first and non-food contents during the second session. Serial blood sampling of ghrelin, leptin, and insulin was performed every 10–15 min throughout the test sessions.

Results: As expected, ghrelin levels increased before each meal, independent of the picture contents. In addition, ghrelin levels during the 30-min interval following the food picture presentation increased significantly compared to the 30-min interval prior to the visual stimulation (AUC 188 vs. 155%, $p < 0.05$). There was no rise in ghrelin after the non-food pictures. The difference between the two picture conditions was significant ($p < 0.05$). Neither picture session affected levels of leptin or insulin.

Conclusion: The authors conclude that food pictures elevate ghrelin levels, while insulin and leptin levels are not affected. Thus, the ubiquitous food cues displayed in today's environment may contribute to increased hunger, food intake and obesity rates via elevations in ghrelin levels.

Visual food cues have been used in multiple studies investing the central regulation of food intake using functional MRI (fMRI). The implementation of this method in the investigation of peripheral processes is more innovative and represents an elegant way of investigating changes of the cephalic phase of food intake. From fMRI studies, it is known that viewing food pictures activates brain areas involved in food anticipation and reward calculation [43]. It has been shown that ghrelin release is regulated by the central nervous system via sympathetic efferences [44, 45]. Vice versa, ghrelin's orexigenic effect is mediated by vagal afferences to the brainstem and hypothalamus [46], and ghrelin is actively transported through the blood-brain barrier [47]. Ghrelin administration increases the neural response to food pictures in areas of appetite control [48]. Through these pathways, ghrelin may represent a link between regulatory brain areas and gut mechanisms when it comes to food anticipation and intake initiation. Its rise in response to visual food cues may denote one of the mechanisms linking environmental factors to eating behavior and increased obesity rates.

Ghrelin mediates food-reward behavior in mice

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J Clin Invest 2011;121:2684–2692

Background: Increased appetite and food intake has been observed in individuals suffering from chronic stress or depression and may contribute to the increased prevalence of obesity in these individuals. There is evidence from animal models and human data that ghrelin might play a role in stress-related eating. However, the underlying mechanisms are incompletely understood.

Methods: In a mouse system, food-reward behavior was assessed using a conditioned place preference (CPP) task after prolonged exposure to chronic social defeat stress (CSDS), a model of psychosocial

stress featuring aspects of major depression and posttraumatic stress disorder. Three different mice were examined: wild-type (WT) mice, ghrelin receptor (GSHR) knockout (GSHR-null) mice, and mice with isolated GSHR expression in catecholaminergic, tyrosine hydroxylase (TH) expressing neurons in the brain (GSHR-null/TH).

Results: WT mice, but not GSHR-null mice, responded to ghrelin injections by increasing their intake of chow. This effect could be restored in the GSHR-null/TH mice. During the CSDS exposure, GSHR-null mice showed increased social isolation compared to the WT and GSHR-null/TH mice. WT and GSHR-null/TH mice, but not GSHR-null mice, demonstrated increased weight gain and CPP for intake of the high-intake diet.

Conclusion: The authors conclude that increased intake and preference for a high-fat diet during social stress is ghrelin-dependent and mediated by signaling in catecholaminergic neurons in the brain.

By crossing GSHR-null mice, which contain a loxP-flanked transcriptional blocking cassette inserted into the GSHR gene, with mice in which Cre recombinase expression is driven by the TH promoter (TH-Cre mice) [49, 50], the authors developed an elegant mouse model to study ghrelin-mediated central nervous and peripheral processes.

With the limitation in mind that mice experiments cannot be directly transferred to humans, the authors provide a possible mechanism linking chronic stress and depression to eating behavior. Psychosocial stress leads to elevations in circulating levels of acyl-ghrelin. As sympathoadrenal tone is increased in stress, speculatively, this stress-induced elevation may involve stimulation of β_1 -adrenergic receptors on ghrelin cells, a pathway that has been implicated in ghrelin release in response to fasting [44, 51]. Ghrelin, in turn, interacts with its receptor, GSHR, which is distributed throughout the brain and periphery [52]. The data in this report suggest that direct ghrelin signaling, specifically on GSHR-TH-coexpressing neurons, is sufficient to decrease social avoidance and induce hedonic eating behavior in mice. The effects on eating behavior led to increased intake of calorically dense foods and increased body weight, a correlate of the observed increased prevalence of obesity in humans with chronic stress or depression.

Food for thought

Neighborhoods, obesity, and diabetes – a randomized social experiment

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Background: There is observational evidence that neighborhood environments may contribute to the development of obesity and diabetes. The association of obesity and diabetes with social environment was studied in a large-scale social experiment by randomly assigning different neighborhood conditions.

Methods: During the timeframe from 1994 to 1998, 4,498 women with children living in public developments in high-poverty areas of Baltimore, Boston, Chicago, or New York were randomly assigned to one of three groups. Families in the intervention group received short-term counseling on housing search plus housing vouchers which had to be used in a low-poverty census tract ($n = 1,788$); a second group received conventional, unrestricted housing vouchers and no additional counseling ($n = 1,312$), and the control group received neither counseling nor vouchers ($n = 1,398$). A long-term follow-up survey was carried out from 2008 through 2010 including measurement of weight status, HbA_{1c} , and health outcomes.

Results: Compared with the control group, participants receiving a low-poverty voucher had lower prevalences of BMI >35 kg/m² (−4.61 percentage points) and BMI >40 kg/m² (−3.38 percentage points) at 10–15 years of follow-up. Furthermore, the prevalence of HbA_{1c} levels $>6.5\%$ was reduced in the intervention group compared to controls (−4.31 percentage points), corresponding to a relative reduction of 21.6%. Observed differences in health outcomes between the low-poverty and conventional voucher group did not reach statistical significance.

Conclusions: Moving from high-level to lower-level poverty neighborhoods was associated with moderate but significant reductions in the prevalence of different degrees of obesity and in the prevalence of diabetes. Although the underlying mechanisms remain unclear, it is reasonable to assume that community level interventions have the potential to improve health.

Obesity research taught us that obesity is a multifaceted, multiorgan disease mainly originating from complex gene-environment interactions. The present study by Ludwig et al. now vividly illustrates that the 'environmental' determinants of obesity are not limited to individual-level factors (e.g. diet and physical activity) but also includes important area-level factors: poverty, segregation, impaired collective efficacy, poor infrastructure, and limited access to higher education. In a large-scale 'social experiment' (which undoubtedly could not have been carried out at least in most Western European countries due to ethical concerns), the authors demonstrate that giving mainly Black and Hispanic families the opportunity of moving from high- to low-poverty neighborhoods ameliorates the prevalence of marked obesity and type 2 diabetes during long-term follow-up. Moving to lower poverty neighborhoods not only improved health outcomes, but also increased the reported collective efficacy as a measure of solidarity as well as the subjective feeling of safety, and furthermore changed the structure of social contacts and friendship. Although the mechanisms responsible for the association of local socioeconomic structures and health outcomes remain to be elucidated, the present study clearly shows that any public health intervention targeted at obesity and diabetes should consider effective social policy measures.

Important for clinical practice

Effects of metformin on body weight and body composition in obese insulin-resistant children – a randomized clinical trial

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Background: Metformin suppresses hepatic glucose production, improves peripheral insulin sensitivity and can induce weight stabilization or moderate weight loss in obese adults. Although small trials reported similar positive effects of metformin in obese adolescents, data on the efficacy of metformin in younger children are missing.

Methods: In a randomized double-blind placebo-controlled trial, 100 markedly obese children and adolescents (mean BMI 34.6 ± 6.6 kg/m², age range 6–12 years) with fasting hyperinsulinemia (insulin ≥ 15 μ U/ml) were randomized to either 1,000 mg metformin or placebo twice daily for 6 months followed by 6 months of open-label metformin treatment. All participating families underwent an accompanying clinic-based lifestyle intervention.

Results: After completion of the 6-month randomized phase, mean BMI (-1.09 kg/m²), mean body weight (-3.38 kg), mean BMI Z-score (-0.07), and mean fat mass (-1.40 kg) were significantly reduced in the metformin group compared to the placebo group. Fasting plasma glucose slightly decreased in the metformin group (-0.88 mg/dl) and increased in the placebo group. Concordantly, HOMA-IR index significantly improved under metformin treatment, whereas first-phase insulin secretion and whole-body insulin sensitivity measured by hyperglycemic clamp remained unchanged between the groups. No serious adverse events occurred, however dose reductions due to side effects of metformin had to be applied in 17% of the children in the intervention group. Continued metformin treatment during the open-label phase did not result in further weight reduction in the metformin group, but subjects who previously received placebo significantly decreased their BMI Z-score.

Conclusions: In the setting of a low-intensity lifestyle intervention program, metformin facilitated a moderate reduction in BMI Z-score and fat mass and improved fasting glucose and HOMA-IR in severely obese, insulin-resistant children.

Metformin was first synthesized in the early 1920s and developed – after a changeful history – into one of the most widely prescribed antidiabetic drugs in the world today. Given the limited short- and long-term efficacy of lifestyle interventions in achieving persistent weight loss in severely obese children and adolescents, there is a continuing interest in developing alternative treatment approaches. Currently – in most countries – there are no approved pharmacologic treatment options available for obese children in the prepubertal age range. As onset and course of pubertal development and associated metabolic changes, e.g. in whole-body insulin sensitivity, may represent an important event in the evolution of cardiovascular disease risk in later life, tailoring interventions for obese prepubertal children could be a rewarding aim. In the present study by Yanovski et al., adding metformin to a basic, low-level lifestyle intervention was proven to be a safe and moderately favorable treatment option for at least a duration of up to 1 year in severely obese children aged 6–12 years. Although the reported changes in BMI Z-score induced by metformin seem to be unimpressive, more importantly metformin stabilized levels of fasting glycemia in contrast to the further increasing fasting glucose levels in the placebo group. This finding may provide a rationale for further investigations exploring the potential preventive effect of early-onset metformin treatment on the risk for developing type 2 diabetes.

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