Obesity and Weight Regulation

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We have been very happy to get 2,049 papers out of our established search strategy in PubMed, which have been saved in our 2013 *Yearbook EndNote* database. We then selected 22 papers which in our mind have been the most exciting ones. The highlights in this year's chapter are publications on the influence of sugar consumption on BMI development, new findings on the development, occurrence and function of brown adipose tissue in humans, recent findings on leptin deficiency and leptin resistance, and finally more insight into the possible role of bariatric surgery as a therapeutic option in adolescents with extreme obesity.

Thus, the present *Yearbook* chapter on obesity and weight regulation covers again a broad research area with some new developments, which we think have the potential for a future breakthrough.

New risk assessment of overweight and obesity

Cardiovascular disease risk in healthy children and its association with body mass index: systematic review and meta-analysis

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Background: Two thirds of the world's population live in countries where obesity-related illness is a significant cause of mortality. However, the effect of obesity on children is currently less well understood. Therefore, this analysis aimed to systematically review available evidence on the magnitude of the association between body mass index and cardiovascular risk in obese children and adolescents.

Methods: Literature research included papers published between January 2000 and December 2011 indexed in PubMed, Embase, EBSCOhost's cumulative index to nursing and allied health literature, and the Web of Science databases. Studies were included in the review if they enrolled healthy children between 5 and 15 years from highly developed countries, were initiated after 1990, used retrospective, cross-sectional, case-control, or RCT study designs, and reported weight and at least one prespecified cardiovascular risk factor. For quality assessment of the systematic review, an adapted risk of bias tool of the Cochrane Collaboration was used.

Results: Meta-analysis included 63 studies of 49,220 children from 23 countries. Systolic, diastolic and 24-hour ambulatory blood pressure was significantly higher in overweight or obese children compared to normal-weight children. Resting systolic pressure was higher in overweight and obese patients (overweight: 4.54 mm Hg; 99% CI 2.44; 6.64; $p < 0.001$; obese: 7.49 mm Hg; 99% CI 3.36; 11.62; $p < 0.001$) as well as diastolic (overweight: 2.57 mm Hg; 1.55; 3.58; $p < 0.001$; obese: 4.06 mm Hg; 2.05; 6.08; $p < 0.001$) compared to normal-weight peers. Similar associations were seen in 24-hour ambulatory systolic blood pressure. Obesity was associated with unfavorable serum lipid profiles characterized by elevated total cholesterol (TC) and triglyceride (Tg) levels (TC 0.15 mmol/l; 0.04; 0.25; $p < 0.001$; Tg 0.21 mmol/l; 0.14; 0.27; $p < 0.001$), and low HDL cholesterol. Furthermore, fasting glucose, insulin and parameters of insulin resistance were significantly higher in obese children than in normal-weight children. For physiological parameters, three studies reported an increased left ventricular mass in obese children compared to normal-weight controls (19.12 g; 12.66; 25.59; $p < 0.001$), an effect which remained significant after adjusting for height (11.29 g/m; 6.49; 16.10; $p < 0.001$).

Conclusions: Overweight and obese children are characterized by an adverse cardiovascular risk factor profile compared with normal weight peers. Risk is rising in tandem with increasing body mass index

and could place a higher burden on affected subjects as previously thought. Current definitions and cut-off levels of risk parameters should be re-evaluated for their appropriateness and reliability in identifying those at-risk for cardiovascular disease.

This thoroughly conducted meta-analysis by Friedemann et al. provides broad insight into the complexity of short-term cardiovascular risk associated with childhood obesity. Compared to normal-weight peers, overweight and obese children and adolescents have higher serum lipids, fasting glucose and insulin, and blood pressure and also an increased left ventricular mass. Moreover, in their meta-analysis, Friedemann et al. confirm the observation of aggravating cardiovascular risk with increasing obesity [1, 2]. This review complements previous work illustrating the long-term cardiovascular risk associated with being obese during – probably critical phases in – childhood and adolescence [1]. Currently, very little is known on the exact pathophysiological mechanisms by which childhood obesity modifies disease risk in adulthood. Even more, it is a matter of controversial debate whether childhood BMI is an independent predictor of cardiovascular morbidity and mortality in later life. In this context, the authors have to be lauded for their strong plea to re-evaluate and to standardize cut-off levels for risk parameters of cardiovascular disease in the pediatric age range. Improving our understanding of the evolution of cardiovascular disease over an individual's life-span will be crucial for the definition of reasonable targets for treatment and prevention, which in turn will facilitate effective intervention for those at risk and prevent ineffective or potentially harmful treatment efforts for those who are not.

Obesity has reached developing countries

Childhood obesity in developing countries: epidemiology, determinants, and prevention

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Background: In many developing countries, recent data show that obesity-related non-communicable diseases are increasing and cross-sectional and secular trends indicate an increase in childhood obesity. The aim of this review was to summarize the cross-sectional prevalence and secular trends, as well as determinants and consequences of childhood obesity in developing countries.

Methods: From 1996 to February 2011, a comprehensive literature search was performed in PubMed and Google Scholar using both obesity-specific terms like 'childhood obesity', 'abdominal obesity in children', 'prevalence', 'nutritional education' and the names of several developing countries. In addition, a hand search for other important references and medical databases was conducted. The originally found 701 articles were critically read by two authors. Criteria for inclusion were: country considered emerging and developing economies according to the IMF list 2010 (International Monetary Fund), adequate sample size, robust trial design, citations, published in good impact factor journals, and done by established research groups.

Results and Conclusions: 163 articles and papers were included in this review. Rapidly changing dietary practices and a sedentary lifestyle have led to increasing prevalence of childhood obesity in developing countries. A high socioeconomic status, residence in metropolitan cities, female gender, unawareness and false beliefs about nutrition, marketing by transnational food companies, increasing academic stress, and poor facilities for physical activity are important determinants of childhood obesity. The most effective strategies to tackle childhood obesity were therapeutic lifestyle changes and maintenance of regular physical activity through parental initiative and social support interventions.

This paper reviews recent data concerning the prevalence of childhood overweight and obesity in developing countries. Analyzing 163 reports, the authors separately documented the prevalences in preschool children (<5 years old) and in schoolchildren and adolescents (5–19 years old). Interestingly,

some developing countries are starting to experience the dual epidemic of over- and undernutrition. The calculated global prevalence of overweight (including obesity) in children aged 5–19 years is 10%, ranging from 5.7% in Pakistan to over 40% in Mexico [3, 4]. The prevalences of obesity reach >15% for instance in Brazil, India, Argentina and Mexico [4–6]. Regarding preschool children, de Onis et al. [7] estimated that 3.3% (or 17.5 million) were overweight in developing countries in 1995, based on data covering 88% of the total population.

Regarding the secular trends, the worldwide prevalence of overweight and obesity in preschool children in developed countries increased from 4.2% in 1990 to 6.7% in 2010, and is expected to reach 9.1% in 2020 (~60 million) [8]. This is in contrast to several Western countries, where stagnation or even decline in childhood overweight and obesity prevalence could be detected in the last few years [1]. Although the prevalences are half of those in developed countries (6.7 and 11.7%, respectively), about 35 million overweight and obese children live in developing countries [8]. Regarding the past two decades, the relative increase has been higher in developing countries compared to developed countries (+65 vs. +48%). An alarming rise in the prevalence of obesity could also be documented among older children and adolescents (5–19 years old) in many developing countries [9–11].

The authors also discussed seven key determinants of childhood obesity in developing countries: (1) unhealthy nutrition, (2) physical inactivity, (3) socioeconomic status (SES), (4) area of residence and urbanization, (5) sociocultural factors and traditional beliefs, (6) age and gender, and (7) endocrine or genetic causes. In contrast to developed countries, high SES was positively related to childhood obesity. The unrestricted access to energy-dense westernized foods, the lack of knowledge about dietary components, the lack of open spaces and playgrounds as well as unsafe neighborhoods, and the number of nutrition-related sociocultural and traditional beliefs (mostly passed down over centuries), especially contribute to the problem.

The final section on the management of childhood obesity discusses how clinically meaningful reduction of overweight in children and adolescents can be better achieved with combined behavioral lifestyle interventions with parental support compared with standard care or self-help [12]. The need for effective interventions starting in infancy as well as high-risk screening and effective health education programs is illustrated by the high prevalence of overweight and obesity in preschool children in developing countries.

Where are the missing genes?

Genome-wide SNP and CNV analysis identifies common and low-frequency variants associated with severe early-onset obesity

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Background: Common and rare variants associated with body mass index (BMI) and obesity can explain only less than 5% of the variance in BMI. Although epistatic and gene-environment interactions may contribute to the unexplained heritability of obesity, it seems likely that a significant fraction is due to unknown loci or established loci that have not yet been fully characterized.

Methods: In this study SNP and copy number variation (CNV) association analyses in 1,509 children with an extreme form of obesity and in 5,380 controls have been performed. 29 SNPs were evaluated in an additional 971 severely obese children and 1,990 controls.

Results: Four new loci associated with severe obesity were identified (LEPR, PRKCH, PACS1 and RMST). In addition, a previously reported 43-kb deletion at the NEGR1 locus was associated with severe obesity and was found to be entirely driven by a flanking 8-kb deletion.

Conclusions: By combining SNP and CNV analysis and focusing on severe obesity, four new obesity susceptibility loci have been identified.

The study of individuals with an extreme phenotype has been shown to be very useful. The authors therefore performed a genome-wide association analysis in 1,509 UK children of European ancestry with severe early-onset obesity and in 5,380 Wellcome Trust Case Control Consortium 2 UK control individuals to identify new associations of common and low-frequency SNPs and CNVs with obesity. They analyzed a total of 2 million SNPs. This led to the identification of 29 loci with preliminary evidence of association with obesity. After validation of these 29 SNPs, 9 genome-wide significant signals in 8 loci have been identified. Interestingly, 3 of these loci mapped in or near PRKCH, PACS1 and RMST have not been previously associated with obesity. These genes are ubiquitously expressed and their role in energy homeostasis is until now unknown. This study identifies a new association with an intermediate-frequency allele in the LEPR gene encoding the leptin receptor. The remaining 4 obesity-associated loci (in or near FTO, MC4R, TMEM18 and NEGR1) have been reported previously [13].

The findings of this study add to the body of evidence suggesting that both common and rare variants around specific genes or loci (LEPR, POMC, MC4R, BDNF and SH2B1) are involved in the pathogenesis of obesity. The study also identified rare single CNVs with a strong association to severe obesity. Interestingly, these rare CNVs delete genes which are involved in the neuronal regulation of energy homeostasis affecting G-protein-coupled receptors.

The bitter truth about sugar

Sugar-sweetened beverages and genetic risk of obesity

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Background: Over recent years, genome-wide association studies have established the association of more than 30 loci with body mass index (BMI) determining susceptibility to overweight and obesity. Increasing consumption of sugar-sweetened beverages is potentially a significant contributor to the obesity epidemic. Whether consumption of sugar-sweetened beverages interacts with genetically determined predisposition to obesity is currently unknown.

Methods: A genetic predisposition score was calculated on the basis of 32 BMI loci associated with obesity. Interaction between genetic obesity predisposition and intake of sugar-sweetened beverages in relation to BMI was analyzed prospectively in men and women from two cohort studies (6,943 women from the Nurses' Health Study (NHS); 4,423 men from the Health Professionals Follow-up Study (HPFS)) and a large replication cohort (21,740 women from the Women's Genome Health Study (WGHS)).

Results: In study participants with a higher intake of sugar-sweetened beverages, genetic association with BMI was stronger than in participants with lower intake. In combined analysis of the NHS and HPFS cohorts, per increment of 10 risk alleles BMI increased by 1.00 for consumption of less than one serving of sugar-sweetened beverages per month, by 1.12 for one to four servings per month, by 1.38 for two to six servings per week, and by 1.78 for one or more servings per day ($p < 0.001$ for interaction). Relative risks for incident obesity per increment of 10 risk alleles increased from 1.19 in the lowest to 5.06 in the highest category of intake ($p = 0.02$ for interaction). Similarly, in the WGHS cohort BMI increases per increment of 10 risk alleles were 1.39, 1.64, 1.90, and 2.53 across beverage consumption categories ($p < 0.001$ for interaction) and the relative risk for incident obesity increased from 1.40 in the lowest to 3.16 in the highest category, respectively ($p = 0.007$ for interaction).

Conclusions: These results suggest that individuals with a more pronounced genetic predisposition to obesity may be more susceptible to the adverse effects of sugar-sweetened beverages on BMI.

Trial of sugar-free or sugar-sweetened beverages and body weight in children

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Background: The potential association of increasing consumption of sugar-sweetened beverages and the risk for obesity and cardiometabolic diseases is a major public health concern. However, currently available evidence supporting a causal relationship between consumption of caloric beverages and obesity remains inconclusive.

Methods: The authors performed an 18-month randomized, double-blind controlled trial including 641 normal-weight children (age range 4–11 years). Study subjects received either 250 ml of a sugar-free, artificially sweetened beverage per day (sugar-free group) or a sweetened caloric beverage providing 104 kcal/day (sugar group) at school. At the end of the intervention period, the dropout rate was 26%. Multiple imputation was used to impute the outcome values for the children who did not complete the study.

Results: Baseline anthropometric characteristics were similar in both study groups. In the course of the study, BMI z-score increased by 0.02 SD units in the sugar-free group and by 0.15 SD units in the sugar group ($p = 0.001$ for difference in change from baseline). Weight gain was 7.37 kg in the sugar group and 6.35 kg in the sugar-free group ($p < 0.001$ for difference in change from baseline). Furthermore, other parameters of body fatness (sum of skinfold thickness, fat mass on electrical impedance, waist-to-height ratio) also showed significantly more pronounced increases in the sugar group than in the sugar-free group.

Conclusions: Replacing sugar-sweetened beverages with non-caloric beverages significantly reduced weight gain and accrual of fat mass in normal-weight children.

A randomized trial of sugar-sweetened beverages and adolescent body weight

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Background: Calories from sugar-sweetened beverages may be an important contributor to excessive weight gain in childhood and adolescence. Currently, evidence is lacking on the effectiveness of interventions aiming at consumption of sugar-sweetened beverages in order to reduce weight gain.

Methods: The authors performed a randomized controlled trial assigning 224 obese adolescents (mean age 15.3 ± 0.7 years) either to an intervention or control group. The intervention group underwent a multicomponent program designed to reduce consumption of sugar-sweetened beverages and included home-delivery of non-caloric beverages. The study duration consisted of a 1-year intervention and 1-year follow-up period.

Results: In the intervention group, consumption of sugar-sweetened beverages declined from 1.7 servings/day at baseline to 0.2 servings/day at 1-year follow-up and 0.4 servings/day at 2-year follow-up ($p < 0.001$). In the control group, consumption of sugary drinks declined from 1.7 servings/day at baseline to 0.9 servings/day at 1-year follow-up and 0.8 servings/day at 2-year follow-up. BMI, the primary outcome, did not differ significantly between the groups at 2 years. Nonetheless, at 1-year follow-up, significant differences could be detected between the groups for weight gain (-1.9 kg, $p = 0.04$) and BMI change (-0.57 , $p = 0.045$). In a subgroup of study subjects with Hispanic ancestry ($n = 46$), significant differences occurred in weight gain (1 year: -6.4 kg, 2 years: -8.8 kg, $p < 0.005$) and BMI change (1 year: -1.79 , 2 years: -2.35 , $p < 0.01$) between the control and intervention group at both follow-up time points.

Conclusions: A 1-year intervention aimed at reduction of consumption of sugar-sweetened beverages resulted in modestly lower gains in BMI and weight compared to controls at 1-year follow-up. Changes were not sustained at 2 years.

The worldwide obesity epidemic is a major challenge for public healthcare systems. Over the past years, the notion of the coincident increase in the consumption of sugar-sweetened beverages with

increasing prevalence rates of overweight and obesity [14] fuelled an emerging public debate on regulatory possibilities to limit consumption of caloric soft drinks especially in children and adolescents. New York City's so-called 'soda rule', which attempted to limit portion sizes of caloric beverages and which has been only recently rejected by a public court ruling due to legislative issues, may serve as a case study for similar public health initiatives in the next years.

Today, in 'westernized' societies sugar intake from sweetened beverages is a major caloric food source, especially in children and adolescents. Caloric drinks are extensively marketed to children and adolescents by focused advertising strategies. 'Liquid calories' may drive greater energy intake and weight gain through flawed satiety signaling and compensatory dietary responses.

As compelling the hypothesis of soft drinks as a major driving force behind soaring obesity prevalence rates may be, as brittle is the currently available evidence supporting it. However, in 2012, three compelling studies published in the *New England Journal of Medicine* shed new light on the case, demonstrating a role for consumption of sugar-sweetened beverages in the development of overweight and obesity under 'free-living', real-world conditions.

First, Qi et al. provide strong evidence for an interaction between intake of sugar-sweetened beverages and genetically determined obesity risk using a cleverly compiled predisposition score. The most important lesson from this study is that excess caloric intake through sweetened beverages exerts its most hazardous effects in those carrying the highest genetic risk.

Second, concurrent papers by Ruyter et al. and Ebbeling et al. present data from randomized controlled trials of interventions that aimed to reduce the consumption of sugar-sweetened beverages in children and adolescents. Ruyter et al. demonstrated that masked replacement of sugar-sweetened soft-drinks with non-caloric soft drinks reduced weight gain and accrual of fat mass in normal-weight schoolchildren. Ebbeling et al. reported the effects of an intervention targeting lifestyle and behavioral habits at the family level using home-delivery of non-caloric beverages. Although observed changes in BMI were only modest in this study, the intervention seemed to have the highest impact on a high-risk group for childhood obesity and its comorbidities – Hispanic youths. These results are closing the circle to the data of Qi et al. on the clear gene-environment interaction which underlies the association of soft drink consumption and development of obesity.

White adipose tissue – a tumor?

Link between adipose tissue angiogenesis and fat accumulation in severely obese subjects

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Background: White adipose tissue (WAT) is a very dynamic organ, being able to expand in times of energy surplus and shrink upon increased energy demand. Each adipocyte is supplied by at least one capillary. The remodeling process in adipose tissue upon weight gain and loss therefore also affects the vascularization. The aim of this study was to find out if the angiogenic capacity of subcutaneous (sc) and omental (om) WAT differentially affects fat accumulation and distribution and also the subsequent development of metabolic disorders in obesity.

Methods: Paired samples of scWAT and omWAT obtained during bariatric surgery were collected from 29 patients, qPCR and immunohistochemical analysis was performed and data were related to metabolic and anthropometric parameters.

Results: A correlation between vascular density in omWAT and waist circumference was detected and between vascular density in scWAT and BMI. Markers of angiogenesis were not associated with metabolic disorders. The mRNA expression of VEGFR2 and also the number of vessels per adipocytes correlated with the adipocyte area in both sc and omWAT. Bariatric surgery-induced weight loss negatively correlated with vascular density and adipocyte hypertrophy and negatively with inflammation and angiogenesis in WAT.

Conclusions: This study shows that angiogenesis is not involved in the development of obesity-induced insulin resistance, but influences WAT expansion and plasticity.

It has long been known that angiogenesis and adipogenesis are linked together. Studying early adipose tissue development in human fetuses in 1965, Wassermann described that capillary structures are visible during the formation of adipose lobuli in early gestation suggesting a close association between both processes [15]. Only very recently, John Graff's laboratory demonstrated [16] that white adipocyte progenitor cells reside within the vascular wall in adipose tissue thereby providing an explanation for the old histological observation.

In that sense it is of utmost importance to gain insights into how obesity affects the vascularization of adipose tissue. Knowing that different adipose tissue depots play different roles in the pathogenesis of obesity-related disorders, it is specifically interesting to learn if angiogenesis is regulated in a depot-specific manner in subcutaneous and omental adipose tissue. The study by Lemoine et al. identified an influence of angiogenesis on adipose tissue expandability.

This raises the questions whether simply targeting angiogenesis in adipose tissue would prevent expansion of adipose tissue. Indeed, several studies have already addressed this question. Mice treated with anti-angiogenic agents displayed a reversible weight reduction and adipose tissue loss [17]. Likewise, the induction of apoptosis specifically in the adipose vasculature by a specific peptide leads to reversal of obesity [18]. The peptide sequence was further modified, then termed 'adipotide' and tested in non-human primates. Treatment with adipotide led to rapid weight loss and improved insulin sensitivity in obese monkeys [19] establishing the concept of killing the adipose vasculature as a new target for the treatment of obesity. From this work one could conclude that obesity can be treated like a tumor by inhibiting blood vessel formation [20–22]. This concept is novel and interesting, but further studies are certainly needed to learn about possible adverse effects, especially under long-term durations probably necessary for the treatment of obesity. Similar studies are needed to understand the relationship between angiogenesis and adipogenesis in human cohorts.

The holy grail of obesity: brown adipose tissue – the story goes on

Evidence for two types of brown adipose tissue in humans

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Background: Until recently, the supraclavicular adipose depot in humans has been considered to be an equivalent of the interscapular brown adipose depot of mice. A recent paper reported that the supraclavicular tissue of humans expressed molecular markers of beige adipocytes, an intermediate cell type which is distinct of classical brown adipocytes.

Methods: Interscapular fat tissue samples from 8 infants were taken postmortem and were compared with supraclavicular and periaxillary adipose tissue regarding brown adipocyte marker expression by immunohistochemistry and quantitative real-time PCR.

Results: Interscapular adipose tissue from infants expresses marker genes which are highly expressed in classical brown adipose tissue of mice. These genes are differentially expressed in adult supraclavicular periaxillary tissues.

Conclusion: The authors conclude that infants' interscapular brown adipose tissue consists of classical brown adipocytes.

Anatomical localization, gene expression profiling and functional characterization of adult human neck brown fat

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Background: Formerly believed to only be present and active in rodents and human infants, brown adipose (BAT) tissue has been also recently shown in adults. It has been suggested that BAT activation could be used as a safe treatment for obesity and metabolic dysfunction.

Methods: Anatomically defined neck fat samples from adult human volunteers were isolated and the expression profile, differentiation capacity and basal oxygen consumption was compared to different mouse adipose depots.

Results: A wide variety of UCP-1 expression levels was found among the different adipose locations with highest expression in close proximity to the musculus longus colli. By comparison of human deep neck and subcutaneous adipose tissue with different mouse adipose depots, expression analysis revealed that some human samples share similarities with classical, also called constitutive, brown fat.

Conclusion: Although the properties of human neck fat vary substantially between individuals, some human samples share many similarities with classical rodent BAT.

Brown adipose tissue (BAT) has long been considered to play a role only in hibernating animals and human infants. However, 6 years ago it was shown that BAT is also present and active in adults and has an effect on the regulation of body composition [24]. Studies in rodents have shown that white and brown adipocytes do not share the same origin and that brown cells derive from a progenitor that also gives rise to muscle cells [25–27]. Even more confusing, brown-like cells with thermogenic properties (beige adipocytes) do not develop from those progenitors but arise from white adipose tissue [27, 28]. So if there are two types of brown fat, we have to ask the question: which type is human BAT? Wu et al. [29] have proposed that human BAT is beige.

These two papers published in *Nature Medicine* take a further look at the origin of human BAT and examine if human BAT is classical brown or beige. The answer is: it depends on which tissue localization you look at. Lidell et al. used magnetic resonance imaging to identify BAT in infants using the fat fraction method. They found that these tissues express *UCP1* as well as another classical BAT marker, *ZIC1*. Thus, infants seem to possess classical brown fat. But what about BAT in adults? Cypess et al. [21] examined different adipose tissue depots in the neck of adults and compared expression patterns. Interestingly, neck fat in humans does not seem to be homogenous, but shows a gradient of brown adipose gene expression increasing from subcutaneous to the inner neck fat with highest *UCP1* and *ZIC1* expression. The authors conclude that the deep neck fat must be classical. The depots between the subcutaneous and the deepest neck fat show intermediated *UCP1* expression and looked like beige depots, however, their true nature was not clear according to gene expression, since there is high variation among individuals. On the other hand, Lidell et al. identified adult peri-adrenal adipose tissue as beige.

These two studies show that, from an evolutionary point of view, humans are not that different from rodents and they still keep a proportion of classical brown fat. This is promising for using brown fat as a therapeutic tool in the future.

Inverse association between brown adipose tissue activation and white adipose tissue accumulation in successfully treated pediatric malignancy

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Background: Brown adipose tissue (BAT) has been suggested to be protective against obesity. The authors studied whether changes in BAT have an impact on subcutaneous adipose tissue (SAT) or visceral adipose tissue (VAT) accumulation in children treated for malignancy.

Methods: 32 cancer patients without BAT activity at the beginning at treatment were analyzed for changes in SAT and VAT from diagnosis to remission. After successful cancer treatment, children with BAT activity (BAT+) were compared to those without BAT (BAT-) activity when free of disease.

Results: After successful treatment of the cancer, BAT was detected in 19 patients, whereas in 13 children, BAT activity was not found. BAT+ patients gained significantly less weight and showed less SAT and VAT accumulation. Multiple regression analysis revealed negative correlation of BAT activation with weight, SAT and VAT even after correction for age, glucocorticoid treatment and season of BAT assessment.

Conclusion: Activation of BAT in children treated for malignancy is associated with less white adipose tissue accumulation.

It has been found in retrospective studies that brown adipose tissue (BAT) appearance is inversely correlated with BMI and body fat [23]. Thus, BAT is a potential target tissue to therapeutically combat obesity. In this longitudinal study, the relationship between BAT activity and white fat accumulation was examined in children treated for malignancies. Children without signs of active BAT at the beginning of treatment were chosen. Compared to studies in adults, this study has the opportunity of shorter treatment periods and higher cure rates. Interestingly, half of the study participants were positive for BAT after remission of the malignancy and these patients had accumulated less body weight, VAT and SAT during cancer treatment. Additionally, glucocorticoid treatment did not have an effect on BAT activity. Recently, the authors have also shown that BAT activity is suppressed in children with lymphoma. However, the mechanism behind the relationship of cancer and BAT activity is not known.

This study provides further evidence that BAT may have a beneficial effect on body composition. It has to be mentioned that the analysis here was done on routine PET scans performed for cancer management. This otherwise quite expensive and invasive method cannot yet be applied in healthy children for study reasons.

Leptin – the voice of adipose tissue

Leptin reverses declines in satiation in weight-reduced obese humans

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Background: Weight reduction leads to lower energy expenditure as well as increased hunger at least partly due to reduced circulating leptin levels and reduced leptin signaling in the central nervous system. The substitution of leptin during and after weight reduction seems to be an obvious approach in order to support sustained weight loss.

Methods: This study examined the hypothesis that reduction in leptin signaling may reduce satiety in humans by investigating the effects of leptin repletion on feeding behavior after weight loss. Ten obese

humans were studied as inpatients while they received a weight maintaining liquid formula diet at each of three time periods: (1) while maintaining their usual weight and then after weight reduction and stabilization at 10% below initial weight; and subsequently while they received 5 weeks of either (2) twice-daily injections of placebo or (3) 'replacement doses' of leptin in a single-blind crossover design with a 2-week washout period between treatments. Satiety was assessed by measuring intake and ratings of appetite-related dispositions 3 h after ingestion of 300 kcal of the liquid formula diet.

Results: This study showed that both energy expenditure and the visual analog scale ratings reflecting satiety were significantly lower on placebo treatment as compared to the earlier period before weight loss or on leptin replacement after weight reduction.

Conclusion: These data show that the absence of leptin signaling after weight loss blunts the expression of feeding inhibition in humans.

It is interesting to see that there are several similarities between the neuroendocrine, autonomic, metabolic, and behavioral changes of weight-reduced individuals and congenitally leptin-deficient individuals. This suggests that the reduction in circulation and central nervous system leptin concentrations that occur during and remain after weight loss (if weight loss leads to a loss of fat mass) are sensed via hypothalamic neurons as the decrease in an inhibitory signal, thereby facilitating energy restoring actions [41, 42]. The hypothesis behind this study was that weight-reduced subjects would demonstrate reduced satiety that would be 'reversed' by leptin supplementation. Therefore, the primary outcome of this study was satiety.

The major finding was that leptin administration to weight-reduced subjects significantly increased satiety as reflected in postmeal feelings of fullness and the perception of how much food was eaten. Postmeal ratings of the amount eaten in relation to switching to another food, after eating essentially the same amounts of food, were significantly higher after leptin administration. The study design included examination of the effects of weight loss and leptin on eating behavior in weight-reduced individuals that was not confounded by changes in diet composition, exercise, lack of weight stability, while minimizing the effects of hedonic aspects of food.

This is the first study to demonstrate that leptin administration to human subjects whose leptin concentrations decreased after weight loss has a similar effect on satiety to those in individuals with congenital leptin deficiency [33, 43, 44]. This study stands also in direct contrast to studies showing a lack of leptin effects in humans at usual body weight [45]. Therefore, this study fills an important 'niche' in the sparse literature regarding the dependence of leptin effects on the nutritional context in which it is administered.

Functional magnetic resonance imaging analysis of food-related brain activity in patients with lipodystrophy undergoing leptin replacement therapy

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Background: Lipodystrophies are rare diseases characterized by a paucity of adipose tissue and low circulating concentrations of the adipocyte-derived hormone leptin. Interestingly, replacement therapy with metreleptin in these patients leads to increased satiety and improvements of metabolic disorders. The aim of the study was to investigate food-related brain activities by means of functional magnetic resonance imaging in patients with lipodystrophy and hypoleptinemia before and after leptin replacement therapy in order to clarify the pathogenic mechanisms of eating disorders in these patients.

Methods: Food-related neural activity was investigated by functional magnetic resonance imaging in patients with lipodystrophy with and without leptin replacement treatment as well as in healthy controls.

Results: Patients with lipodystrophy showed an insufficient postprandial suppression of neural activity in the amygdala, insula, nucleus accumbens, caudate, putamen, and globus pallidus when compared to controls. Leptin treatment effectively suppressed neural activity in many of these regions.

Conclusion: This study demonstrates the insufficiency of postprandial suppression of food-related neural activity in lipodystrophic patients. This deficiency was effectively restored by leptin. The study emphasizes the important pathological role of leptin in eating disorders in lipodystrophy.

Earlier studies have shown that leptin replacement therapy with metreleptin effectively improved metabolic disorders in patients with lipodystrophy [46–48]. In these studies it has also been observed that metreleptin suppresses appetite [49, 50]. Recent studies showed that functional neuroimaging techniques provide novel insights into homeostatic and hedonic aspects of human eating behavior. But previously there was no comparison of eating behaviors between healthy subjects and patients with lipodystrophy. Therefore, also age- and sex-matched healthy subjects were included into this study.

The results showed that suppression of neuronal response to food-specific stimuli after a meal is attenuated in patients with lipodystrophy compared with healthy subjects. In addition, the formation of a satiety feeling after a meal is also attenuated in patients with lipodystrophy compared with healthy subjects. Leptin replacement therapy enhances the suppression of neuronal response to food-specific stimuli after a meal in patients with lipodystrophy. The enhanced formation of satiety after a meal in patients with lipodystrophy by leptin replacement therapy is consistent with the results of the functional MRI analysis.

This is the first report that demonstrates the difference in food-related neural activity between patients with lipodystrophy and healthy controls. Interestingly, a significant difference in food-related neural activity between patients and controls was detected in many brain areas under the postprandial conditions but in only a few brain areas under the fasting conditions. Leptin replacement therapy effectively restored neural activity in many brain areas under the postprandial conditions in patients with lipodystrophy.

This is also the first report that demonstrates the difference in appetite between patients with lipodystrophy and healthy controls. Postprandial satiety was significantly reduced in the patients, whereas there was no apparent difference in hunger under the fasting condition. Because leptin replacement therapy effectively increased postprandial satiety and did not affect hunger under the fasting in patients, leptin deficiency in patients accounts for a large part of the difference in postprandial satiety between patients and controls.

Challenges and opportunities of defining clinical leptin resistance

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Background: The term ‘leptin resistance’ is widely used. However, there is no clear definition of this clinical condition.

Methods: The National Institute of Diabetes and Digestive and Kidney Diseases at the National Institute of Health held a workshop on this issue with the aim to explore current usage of the term ‘leptin resistance’ and to work towards a quantifiable, clinically useful definition that could be used to identify specific patient populations.

Results: Currently there is no universal, quantifiable, and clinically useful definition of the term ‘leptin resistance’. Further advances require biomarkers that can be used to identify patients who may benefit from leptin therapy and that are useful for understanding the determinants of clinical leptin responsiveness.

The term ‘leptin resistance’ arose not long after the discovery of leptin in 1994. ‘Leptin resistance’ may either indicate the state of obesity in the face of hyperleptinemia or the failure of pharmacologic leptin to suppress feeding.

Leptin, a 16-kDa cytokine, is produced by adipose tissue in approximate proportion to adipose tissue mass. Circulating leptin levels reflect therefore the status of long-term adipose tissue energy stores, and these levels are greater in obese compared to lean individuals. Adequate fat stores and leptin concentrations should diminish the drive to feed, and enable energy expenditure in a physiological

way, while inadequate or decreasing fat stores and leptin concentrations increase the desire to eat and decrease energy utilization. Leptin also is an important hormone for reproductive function and also for immune function. In addition, some metabolic effects of leptin seem to be independent on its effect on body weight regulation [30–40]. These biological effects of leptin suggest its potential therapeutic utility in a variety of pathologic states. However, in most forms of obesity an apparently diminished metabolic efficacy of leptin is observed and leptin therapy for obesity or obesity-related comorbidities is usually ineffective.

This paper summarizes the outcome of the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institute of Health (NIH) workshop that aimed to produce a clinical definition of 'leptin resistance'. The paper summarizes data on leptin biology as well as on mechanisms leading to leptin resistance. Furthermore, published data on clinical issues related to leptin resistance as well as clinical leptin responsiveness are discussed.

While no universal, quantifiable, and clinically useful definition of the term 'leptin resistance' is yet possible, defining populations of patients and/or disease processes that are potentially responsive to leptin therapy will be important. Leptin treatment has proven therapeutically useful for several clinical indications, including lipodystrophy syndromes, and is likely to be useful for numerous others. Identifying predictors of leptin responsiveness represents an important research priority.

Is there a hope for new drugs?

Exenatide as a weight loss therapy in extreme pediatric obesity: a randomized, controlled pilot study

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Background: Pediatric and adolescent extreme obesity are distinct from simple obesity as they are associated with high comorbidity rates and are resistant to lifestyle interventions. Thus, alternative treatment options are needed. While adolescent bariatric surgery is on the rise, pharmacologic interventions are less invasive and should be given consideration in this patient group. Exenatide is a glucagon-like peptide-1 receptor agonist used in T2DM treatment. In adults, exenatide reduces BMI, body weight and body fat via appetite suppression, leading the authors to explore its effects on BMI and cardiometabolic risk factors in youth.

Methods: 12 patients, 9–16 years of age, with extreme obesity (BMI ≥ 1.2 times the 95th percentile or BMI ≥ 35 kg/m²) were enrolled in a 6-month, randomized, open-label, crossover, trial. Each subject completed a 3-month control phase of lifestyle modification and a 3-month intervention phase of lifestyle modification plus exenatide. The intervention order was randomized. The outcomes BMI (primary), body fat percentage, blood pressure, lipids, oral glucose tolerance tests (OGTT), adipokines, plasma biomarkers of endothelial activation, and endothelial function were assessed at baseline and after each intervention.

Results: Compared to the lifestyle intervention alone, exenatide significantly reduced BMI (-1.7 kg/m², 95% CI -3.0 , -0.4 ; $p = 0.01$), body weight (-3.9 kg, 95% CI -7.11 , -0.69 ; $p = 0.02$), and fasting insulin (-7.5 mU/l, 95% CI -13.71 , -1.37 ; $p = 0.02$). Significant improvements were observed for OGTT-derived insulin sensitivity ($p = 0.02$) and β -cell function ($p = 0.03$). Exenatide was generally well tolerated (the most common adverse event was mild nausea in 36%).

Conclusion: The authors conclude that there is preliminary evidence that exenatide reduces BMI and body weight and that its application and side-effect profile are tolerated by obese youth. Thus, exenatide is a potential candidate agent for weight loss therapy in extreme pediatric obesity and should be evaluated further in larger, well-controlled trials.

Pediatric and adolescent extreme obesity are distinct from simple obesity as they are associated with high comorbidity rates and are resistant to lifestyle interventions [51]. Few weight loss drugs have been evaluated in children and adolescents and this is the first study to examine the effects of a glucagon-like peptide-1 receptor agonist in obese youth. In adults, exenatide reduces BMI, body weight and body fat [52, 53] via appetite suppression, leading the authors to explore its effects on BMI and cardiometabolic risk factors in youth. The observed BMI reduction of -1.7 kg/m^2 is promising and calls for larger, longer-term trials. As with any other conventional or pharmacologic intervention, the main question remains whether weight loss can be sustained in the long term, or if rebound is expected after discontinuation of therapy. Hinting in that direction, the authors detected an order effect with a trend toward larger BMI increases during the control phase when it was preceded by exenatide. These results could represent a rebound phenomenon and are in line with previous studies of orlistat and metformin, which reported weight regain after discontinuation of the medication. Larger trials are warranted to explore the long-term safety and efficacy of exenatide.

Pharmacotherapy for childhood obesity: present and future prospects

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Background: Lifestyle modification interventions including behavioral treatment, diet modification, and physical activity are the cornerstones of the treatment of obesity in children and adolescents. Such interventions have shown, however, relatively limited success. There is considerable interest in combining lifestyle modification programs with more intensive strategies, including pharmacotherapy, to ameliorate obesity in children and adolescents.

Methods: This review article summarizes the literature on the safety and efficacy of medications that have been studied for the treatment of obesity in children and adolescents. In addition, comments to drugs under development for treatment of obesity in adults are provided. A total of 1,296 articles were identified by a PubMed search and have been examined.

Results: This review summarizes the study designs and clinical results achieved with each drug, with the discussion of methodology including subject characteristics, type, and duration of intervention, and adverse effects.

Conclusions: Published evidence on pharmacotherapy for pediatric obesity is relatively sparse. At present only one agent (orlistat) holds FDA approval to treat obesity among adolescents age 12–16 years; no weight loss medications are approved for use in children below age 12.

Although the literature on pharmacotherapy in childhood obesity is sparse and only one agent (orlistat) is approved for treatment, this review is a valuable summary of published data on pharmacological efforts in obese children and adolescents, and provides a comprehensive overview on the current pharmacotherapeutic options. These options comprise drugs known to decrease energy intake (classical centrally acting anorexiants), drugs in development that may act centrally as anorexiants, drugs that affect nutrient trafficking (gut digestion or renal nutrient reabsorption), drugs that affect metabolism (insulin action, lipolysis, or energy expenditure), as well as new combination therapies.

Lifestyle modification interventions including behavioral treatment, diet modification, and physical activity are the cornerstones of the treatment of obesity in children and adolescents [54]. Effective pharmacotherapy that reverses excessive adiposity and improves obesity-related comorbid conditions in pediatric patients remains elusive. So far, the weight management impact of available drugs (in adults) has been modest. Because of the importance of the metabolic pathways involved in the regulation of energy balance, it is also unlikely that any highly effective weight loss medication will be risk-free. Therefore, careful evaluation is required to balance the potential known and unknown adverse effects against the potential benefits of anti-obesity medications in an individual.

Nevertheless, there is great hope that development of more effective, etiology-based anti-obesity therapies for children and adults will prove possible. The value of using a specific treatment directed

towards an established obesity-causing mechanism has already been shown for children and adolescents with one extremely rare form of monogenic obesity: metreleptin is remarkably successful to treat the obesity of leptin deficiency [30, 31, 33, 55]. It seems likely, therefore, that once a more complete differential diagnosis for pediatric obesity can be established based on genetic (and perhaps epigenetic) and phenotypic characteristics, new drug trials can be initiated that select patients who are more likely to respond to a given medication.

Cluster analysis of the national weight control registry to identify distinct subgroups maintaining successful weight loss

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Obesity 2012;20:2039–2047

Background: The National Weight Control Registry (NWCRC) is an ongoing, observational study of individuals who have achieved successful weight loss maintenance (at least 13.6 kg/30 lb). Cluster analysis considers factors such as weight and health history, satisfaction with maintaining weight, as well as other psychological factors and demographic variables. The characteristics of these clusters could inform different strategies and attitudes regarding weight, weight maintenance and weight loss and can ultimately be used to develop individualized weight management programs.

Methods: Registry members self-reported data on social, demographic, dietary, physical activity and weight loss characteristics. Cluster analysis automatically excludes missing data. Resulting factor items were included in latent class cluster analysis using Latent Gold 3.0.6 allowing a mixed measurement level calculation of individual questionnaire scores to identify unique clusters. From 1998 to 2002, 2,228 participants were included in the analysis.

Results: Cluster I represented weight-stable, healthy, and exercise-conscious NWCRC participants (1,125/50.5%) characterized by a high level of satisfaction with current weight status. Participants in cluster II (599/26.9%) were characterized as ‘struggling’ with problems of weight maintenance since childhood (maximum lifetime BMI was 44 kg/m² in this group). Subjects in cluster II showed best resources to lose and maintain weight, but reported more stress, illness and depression. By contrast, participants classified in cluster III, the ‘immediate and long-term success’ group (283/12.7%), reported success in weight reduction on the first attempt, least difficulties in maintaining weight or the longest success in holding achieved weight loss. Finally, cluster IV individuals were ‘less physically active’ (221/9.9%), being the oldest (mean age 53.3 years) and less educated with a higher BMI at entry and during lifetime. Cluster IV reported more common health problems.

Conclusions: Sustaining weight loss after obesity intervention is a challenge which calls for individualized approaches rather than a ‘one size fits all’ strategy. Cluster analysis may be a valuable tool to tailor to the specific characteristics of an individual.

Talking to clinicians involved in providing obesity intervention programs leaves you with two major impressions. Most of the doctors are well-versed pragmatists caring for their patients and refusing to surrender to the challenges of lifetime stories of weight-cycling and overwhelming frustration with weight status. But also, many of the obesity clinic doctors admit that they would love to have the chance to look into some kind of crystal ball in order to assign each of their patients to an individualized level of effective intervention. This underlying insecurity in making adequate choices from the therapeutic arsenal for an individual patient is even truer for pediatricians caring for obese children. ‘First do no harm’ is the pledge that has to be fulfilled. As easily determinable predictive markers of treatment response (e.g. as ‘prednisone response’ or ‘minimal residual disease’ in pediatric oncology) are not likely to be available for obesity interventions any time soon, the present study by Ogden et al. gives us food for thought on statistical methods to stratify our patients into clusters, which could help assign each patient (and his family) to individualized treatment approaches.

All bariatric surgeries are not created equal: insights from mechanistic comparisons

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Background: Despite important scientific advances in our understanding of the control of energy balance and body weight regulation, treatment of obesity continues to be a major challenge. The difficulty in maintaining long-term weight loss by means of changes in lifestyle with or without supportive pharmacological treatments reflects the strongly conserved nature of the homeostatic regulatory mechanisms protecting body weight. Given this relatively bleak picture, it is not surprising that bariatric surgery has increased in popularity due to its ability to produce long-term weight loss that is superior to traditional treatments in both magnitude and durability. In addition, some bariatric surgical procedures have an additional positive effect on metabolism, cardiovascular diseases, and cancer risk reduction. The aim of this comprehensive review was to summarize evidence on the mechanisms explaining the favorable health effects of bariatric surgery and to compare the different procedures.

Methods: Published evidence on mechanisms for weight loss after vertical sleeve gastrectomy (VSG), Roux-en-Y gastric bypass (RYGB), and adjustable gastric banding (AGB) were chosen and summarized.

Results: Based on human and animal model literature it has been shown that neither RYGB nor VSG are primarily restrictive procedures. Rather, changes in behavior and physiology indicate that both surgeries alter the defended level of body weight. Furthermore, RYGB and VSG are associated with metabolic improvements that are distinct from those that are caused by weight loss alone.

Conclusions: In order to advance the understanding of the procedures, it is necessary to group bariatric procedures not on the basis of surgical similarity but rather on how they affect key physiological variables. The changes in body energy homeostasis and metabolism after bariatric surgery is mainly caused by alterations in the secretion of gut hormones (ghrelin, cholecystokinin (CCK), glucagon-like peptide-1 (GLP1), peptide YY (PYY)) and changes in intestinal gluconeogenesis, circulating amounts of bile acid as well as changes in ingestive behavior, food choice, food tolerance, taste acuity, and food reward.

Bariatric surgery is able to produce long-term weight loss that is superior to traditional weight loss treatments in both magnitude and durability. Additionally, some bariatric procedures reduce overall mortality despite the inherent risk of surgery itself [56, 57]. Reduced incidences of diabetes, heart disease, and cancer have been reported following bariatric surgery. The effects on some of these elements are powerful enough that pharmacological treatment for diabetes and other elements of the metabolic syndrome such as hyperlipidemia and hypertension can often be discontinued after surgery. This review discusses possible underlying mechanisms responsible for the metabolic benefits of bariatric surgery beyond weight loss with special focus on lipid homeostasis and cardiovascular risk reduction, and glucose homeostasis. The review explains how gastric volume restriction, alteration in gastric emptying influence control of energy balance on the level of the central nervous system as well as energy expenditure. A special focus is laid on the role of gut hormones and other peripheral players. Finally, the impact of changes in intestinal gluconeogenesis and bile acid concentrations in circulation are summarized. A separate chapter of this review is devoted to changes in ingestive behavior induced by the different bariatric surgical procedures.

In the future, it will be important to group bariatric surgical procedures not only on the basis of surgical similarity but also on their physiological and metabolic implications. In this way, it can be possible to optimize the success of a given procedure by tailoring the type of surgery to the patient's individual metabolic derangements. A better understanding of the effects of bariatric surgical procedures on sustained weight loss based on changes in energy homeostasis of the body as well as on metabolism will also help to develop new pharmacological treatments, e.g. interfering with the secretion and action of gastrointestinal hormones.

Two-year outcome of laparoscopic Roux-en-Y gastric bypass in adolescents with severe obesity: results from a Swedish Nationwide Study (AMOS)

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Background: Adolescent extreme obesity is a particular medical challenge, as the affected youth are at risk for early mortality, somatic and psychiatric comorbidities. Thus, treatment options for sustained weight loss and reversion of comorbidities are urgently needed. Bariatric surgery is the only treatment that achieves these goals in adults with morbid obesity, but is not generally endorsed in pediatric patients. The authors aimed to determine if gastric bypass surgery, the most commonly applied procedure in adolescents, is safe and effective for this age group.

Methods: A prospective intervention study was conducted in 81 adolescents (13–18 years). Patients were enrolled over a 3-year period, and were followed for 2 years postoperatively. Laparoscopic gastric bypass surgery was performed at three university hospitals in Sweden. Weight change was compared with adults undergoing the same procedure ($n = 81$) and adolescents receiving combined behavioral weight loss therapy ($n = 81$). Secondary endpoints were metabolic risk factors and quality of life in adolescents undergoing bariatric surgery.

Results: Retention rate was excellent with 100% in both surgical groups and 73% in the non-surgical patients. In adolescents undergoing surgery, BMI was 45.5 ± 6.1 (mean $\pm$ SD) at baseline and 30.2 (95% confidence interval 29.1 – 31.3) after 2 years ($p < 0.001$) corresponding to a 32% weight loss and a 76% loss of excess BMI. The 2-year weight loss was 31% in adult surgery patients, whereas 3% weight gain was seen in conventionally treated adolescents. At baseline, fasting hyperinsulinemia (>20 mU l⁻¹) was present in 70% of the adolescent surgery patients, which was reduced to 0% at 1 year and 3% at 2 years. Other cardiovascular risk factors were also improved. The prevalence of psychopathology was as high as 60%, which is in line with findings in other cohorts of adolescent with extreme obesity. Nevertheless, the treatment was generally well tolerated and, overall, quality of life increased significantly. Adverse events were seen in 33% of patients.

Conclusion: The authors conclude that weight reduction and safety profile of gastric bypass surgery is similar in adolescents and adults. Despite the high prevalence of psychosocial dysfunction, adolescents complied with follow-up visits and experienced benefits on health and quality of life. Due to the challenges inherent to the adolescent population, surgical and psychological challenges require careful attention.

Short-term psychological outcomes in severely obese adolescents after bariatric surgery

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Background: Bariatric surgery encompasses major lifestyle and body changes. When considering this procedure in adolescents, it is important to mind the intense psychosocial adjustment and development that is inherent to this age group. In addition, especially adolescents with extreme obesity have high rates of psychiatric and psychosocial pathology that may be affected by the procedure in either direction. The authors aimed to determine the effect of Roux-en-Y gastric bypass, the most commonly used bariatric procedure in this age group, on adolescents' psychological health.

Methods: Baseline status and short-term changes in anxiety, depression, anger, disruptive behavior, and self-concept were assessed via validated questionnaires (Beck Youth Inventories) at inclusion and 4 months after undergoing Roux-en-Y gastric bypass in 37 adolescents (mean age 16.6 ± 1.3).

Results: Internalizing (anxiety and depression) and externalizing (anger and disruptive behavior) symptoms were higher at baseline than gender-specific norms, which is in line with previous reports 20% had a very low self-concept. Four months after surgery, patients showed significantly fewer symptoms

of anxiety and depression and significantly improved self-concept from baseline. Anger and disruptive behavior showed no significant changes. An analysis of clinically meaningful changes was conducted, and besides the overall positive outcome, 16% (n = 6) of the adolescents had deteriorated on two or more inventories shortly after surgery. No factors predicting this adverse effect could be identified.

Conclusion: The authors endorse the importance of psychological monitoring after bariatric surgery and the need for available psychosocial support for adolescents. Further studies with larger samples are necessary to identify predictors of adverse psychological outcomes in adolescents after bariatric surgery.

Bariatric surgery is the only effective intervention to achieve long-term weight loss, reverse comorbidities, and thereby reduce mortality in adults with extreme obesity. Owing to these favorable outcomes, the use of bariatric surgery in adolescents with extreme obesity has increased worldwide, and between 1997 and 2003 annual procedures in the USA have increased 5-fold from 51 to 282. While bariatric surgery is considered experimental in adolescents, there is early evidence that timely surgical interventions may be favorable, and international guidelines have emerged. Weight loss averages at around 30% in adults and adolescents likewise, and is maintained. Thus, the otherwise routinely observed pronounced weight gain during adolescence would be prevented, allowing weight stabilization at a lower level. As in adults, comorbidities improve after adolescent bariatric surgery, potentially reducing mortality. Moreover, there is evidence that life-threatening comorbidities resolve at higher rates in young patients, and only 19% of adolescents versus 41.3% of adults have persistent hypertension [61] after surgery. In addition, operated adolescents may experience improved mental health in terms of depression, anxiety, self-image, and health-related quality of life.

Notwithstanding these benefits, adolescents have unique physiologic and psychosocial implications that mandate special care, and unanswered questions regarding the safety and efficacy of bariatric surgery in this age group remain. Specific concerns relate to the inability to obtain appropriate consent, the dependence on a caregiver, the risks of elective major surgeries, long-term compliance, and unknown long-term effects. In addition, there may be adverse effects on psychiatric conditions and psychosocial well-being, as described in the study by Järholm et al. When considering bariatric surgery in adolescents, it is important to mind the intense psychosocial adjustment and development that is inherent to this age group. In addition, especially adolescents with extreme obesity have high rates of psychiatric and psychosocial pathology [58, 59] that may be affected by the procedure in either direction [60]. Owing to these challenges and the paucity of long-term outcome data, the role of bariatric surgery in adolescents remains controversial and structured longer-term evaluations of medical and psychosocial implications are needed. The study by Olbers et al. represents one of the largest cohorts of patients undergoing bariatric surgery and reports the second longest follow-up period to date. Ongoing studies, e.g. in the USA (TeenLABS) and Germany (BMBF Consortium 'YES'), will further close this knowledge gap. Pending long-term outcome data, treatment decisions have to be made on an individual basis, and patients should be treated by specialized multidisciplinary teams.

Bariatric surgery following treatment for craniopharyngioma: a systematic review and individual-level data meta-analysis

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Background: Craniopharyngiomas are rare pediatric tumors located in the hypothalamic and/or pituitary region. Due to this location, hypothalamic damage is commonly caused by the tumor or the associated therapy, leading to development of 'hypothalamic obesity'. Hypothalamic obesity is associated with rapid weight gain, eating disorders and high comorbidity rates, and is notoriously difficult to treat. The authors aimed to determine the 12-month outcome of bariatric surgery in patients with hypothalamic obesity as a sequel of craniopharyngioma.

Methods: A systematic review and meta-analysis was performed. Relevant studies were identified by searches of the MEDLINE and EMBASE databases until January 2013.

Results: A total of 21 cases were identified: 6 with adjustable gastric banding (LAGB), 8 with sleeve gastrectomy (SG), 6 with Roux-en-Y gastric bypass (RYGB), and 1 with biliopancreatic diversion (BPD). After 6 months, weight had decreased by 10.5% in the LAGB group, by 20.7% in the SG group, by 18.6% in the RYGB group, and by 11.3% for the BPD patient. After 12 months, weight loss from baseline was 6.1% in the LAGB group, 19.6% in the SG group, 20.2% in the RYGB group, and 24.8% for the BPD patient.

Conclusion: This is the largest report on bariatric surgery in patients with craniopharyngioma. The authors conclude that significant weight loss can be achieved and propose larger studies to establish the best surgical technique for these patients as well as appropriate selection criteria.

Bretault et al. nicely summarize the few published reports on bariatric surgery in patients with craniopharyngioma associated hypothalamic obesity. It is notable that weight reduction is less pronounced compared to those in the above reports of similar procedures in extremely obese adolescents without hypothalamic pathology. Especially in the LAGB group, there is minimal sustained benefit. While RYGB appears to have the most favorable outcomes, it has to be taken into consideration that these reports are pooled from various centers and settings, the numbers are so far small, and other factors may have contributed to the differential outcomes.

Clinical correlates of the weight bias internalization scale in a sample of obese adolescents seeking bariatric surgery

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Background: The Weight Bias Internalization Scale (WBIS) was developed to separate external from the more harmful internalized weight bias and has excellent reliability and validity in adults. This 11-item self-report scale measures the degree to which a respondent believes that negative stereotypes about overweight and obese persons are applicable to him or her. The authors aimed to evaluate the WBIS in obese adolescents seeking bariatric surgery, a particularly high-risk population.

Methods: Psychiatric evaluations, validated self-report questionnaires including the WBIS and other measures of psychopathology, and physical assessments were performed in 65 adolescents enrolled in a bariatric surgery program prior to the surgical intervention.

Results: The WBIS had high internal consistency (Cronbach's $\alpha = 0.92$). The scale had significant partial correlations with depression ($r = 0.19$), anxiety ($r = 0.465$), social, and behavioral problems ($r = 0.364$), quality of life ($r = -0.480$), and eating ($r = 0.579$), shape ($r = 0.815$), and weight concerns ($r = 0.545$). However, WBIS scores did not predict current or past psychiatric diagnosis or treatment or past suicidal ideation. Overall, the WBIS had excellent psychometric properties in a sample of obese treatment-seeking adolescents and correlated significantly with levels of psychopathology.

Conclusion: These findings suggest that the WBIS could be a useful tool for healthcare providers to assess internalized weight bias among treatment-seeking obese youth.

The reported high prevalence of psychosocial pathology in youth with extreme obesity is unexplained, but a correlation with experiences of weight-based stigmatization and teasing has been reported [60]. While other stigmatized groups tend to demonstrate 'in-group' preferences, overweight and obese individuals lack these favorable attitudes [62] and are prone to internalize negative weight-based stereotypes. These internalized stereotypes are proposed to be an important contributing factor to the observed negative psychological outcomes [63]. The study validates WBIS in treatment-seeking adolescents with extreme obesity, providing a new tool to identify adolescents with high internal stigmatization that stand to benefit from appropriate counseling. In conjunction with existing research, the study finds that internalized weight stigmata are associated with elevated levels of psychopathology, but more work is needed to understand the ways in which the internalization of weight stigma influences behaviors and impacts long-term psychological and health outcomes among adolescents.

Prevalence of severe obesity among New Zealand adolescents and associations with health risk behaviors and emotional well-being

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Background: The literature regarding the effects of obesity on mental health and well-being is inconsistent. For the special subgroup of severely obese young people, additional physical and psychosocial health concerns have been described in the USA. This study aimed to describe the current prevalence of severe obesity among adolescent schoolchildren in New Zealand and to determine its association with indicators of mental well-being and risk-taking behaviors.

Methods: 9,107 randomly chosen secondary school students from 96 schools participated in the national health survey Youth'07 in 2007. Weight and height were measured by trained research staff, and severe obesity was defined by the IOTF classification system. During the school day the students provided responses to 622 items assessing the health and well-being of adolescents anonymously using internet tablets and headphones.

Results: 2.5% of the students were defined as severely obese with no difference in the prevalence by sex or age. Weight-related concerns and behaviors were more common among students with severe obesity. Students with severe obesity were more likely to be current smokers (3.9 times more), to engage with health-compromising behaviors, to engage in unhealthy weight control behaviors (i.e. vomiting 1.9 times more and skipping meals 2.6 times more), and to have been bullied at school (1.7 times more) or by their family (3.3 times more) compared with healthy-weight students. With regard to mental health indicators and health-risk behaviors, no differences between students with severe obesity and students with a healthy weight were found.

Conclusions: When working with severely obese adolescents, clinicians should discuss issues of bullying and healthy weight control strategies with the young people and their families.

This study shows recent prevalence data of severe obesity among New Zealand adolescents. At 2.5%, the prevalence is lower compared to the findings in the USA (3.4% of 12- to 19-year-olds [64] or 7% of 12-year-olds [65]). However, this difference was explained by the use of different definitions of severe obesity. Furthermore, the authors observed a social and ethnic gradient in the prevalence of severe obesity for New Zealand young people, which is consistent to the patterns of obesity in New Zealand in general.

It is disturbing that severely obese young people are more likely to experience bullying about their weight at school, by their friends or family, and being called hurtful names. The known association between obesity and experience of bullying [66] is hereby extended to severely obese adolescents. The severity of bullying was investigated by Kim and Leventhal [67] in 2008 who found a significant risk of suicide for young people being bullied. However, the relationship between severe obesity, experience of bullying and mental health indicators could not be confirmed by this study. This result reflects the described mixed outcomes of cross-sectional and longitudinal studies of emotional well-being among obese and severely obese adolescents.

Unhealthy weight-control behaviors are a risk factor for later onset of eating disorders, poor mental health, and ongoing weight gain [68–71]. This is the first large study to demonstrate an even greater burden of poor weight-related beliefs and unhealthy dieting behaviors for young people with severe obesity, compared to overweight and obese young people. Among severely obese young people, an increased risk of smoking was also found in previous studies [72]. The reasons are still unclear – possible reasons are ‘smoking for weight loss’ or being ‘in’. Except for smoking, no difference in health-risk behaviors between severely obese and healthy weight young people could be observed. A post hoc analysis revealed a much greater associations between severe obesity and weight-related beliefs and behaviors for males than for females. This variation by sex was also described in 2010 [66].

The authors concluded that young people with severe obesity are at particular risk for bullying and unhealthy weight control behaviors, but interestingly, apart from smoking, are similar to healthy weight young people on indicators of emotional well-being and other risk-taking behaviors.

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