Obesity and Weight Regulation

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Obesity and its comorbidities are a leading world health concern for which few effective treatments exist. The increasing number of obese children throughout all developed countries has lead policy makers to rank it as a critical public health threat. In the last 12 months several countries have implemented the recommended actions and have involved multiple stakeholders from diverse segments of society and have built up platforms on nutrition and physical activity (e.g. EU Platform on Diet, Physical Activity and Health, <http://europa.eu.int>; fig. 1).

As one example for recommended actions, table 1 shows the immediate steps for confronting childhood obesity as proposed by the US Institute of Medicine (IOM) (www.iom.edu). The final report from the IOM entitled 'Preventing Childhood Obesity: Health in the Balance' was released on September 30, 2004. Further recommendations are also given by the International Obesity Task Force (see www.who.int).

Fig. 1.

Table 1. Immediate steps for confronting the epidemic of childhood obesity as proposed by the US Institute of Medicine (IOM)

Federal Government

- Establish an interdepartmental task force and coordinate federal actions
- Develop nutrition standards for foods and beverages sold in schools
- Fund state-based nutrition and physical-activity grants with strong evaluation components
- Develop guidelines regarding advertising and marketing to children and youth by convening a national conference
- Expand funding for prevention intervention research, experimental behavioral research, and community-based population research; strengthen support for surveillance, monitoring, and evaluation efforts

Industry and Media

- Develop healthier food and beverage product and packaging innovations
- Expand consumer nutrition information
- Provide clear and consistent media messages

State and Local Governments

- Expand and promote opportunities for physical activity in the community through changes to ordinances, capital improvement programs, and other planning practices
- Work with communities to support partnerships and networks that expand the availability of and access to healthful foods

Health-Care Professionals

- Routinely track body mass index (BMI) in children and youth and offer appropriate counseling and guidance to children and their families

Community and Nonprofit Organizations

- Provide opportunities for healthful eating and physical activity in existing and new community programs, particularly for high-risk populations

State and Local Education Authorities and Schools

- Improve the nutritional quality of foods and beverages served and sold in schools and as part of school-related activities
- Increase opportunities for frequent, more intensive, and engaging physical activity during and after school
- Implement school-based interventions to reduce children's screen time
- Develop, implement, and evaluate innovative pilot programs for both staffing and teaching about wellness, healthful eating, and physical activity

Parents and Families

- Engage in and promote more healthful dietary intakes and active lifestyles (e.g., increased physical activity, reduced television and other screen time, more healthful dietary behaviors)
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Modifying sectors in the so-called obesogenic environment should lead to long-term weight loss and maintenance of body weight or should be able to prevent the development of obesity. Besides this important development in the last 12 months further important scientific results were obtained in the field of obesity in children and of body weight regulation. Only manuscripts published in journals with an impact factor of >2 were considered assuming that important and relevant findings were published in these journals [1]. The top findings of the last year again reflect the high quality of research in this field.

New mechanisms

Enhanced leptin sensitivity and attenuation of diet-induced obesity in mice with haploinsufficiency of *Socs3*

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Background: Leptin is a hormone secreted by adipocytes and is able to regulate energy balance by acting on specific hypothalamic pathways. It is suggested that obesity in men and rodents is associated with central leptin resistance. Suppressor of cytokine signaling-3 (*Socs3*) is a leptin-induced negative regulator of leptin receptor signaling and probably a mediator of leptin resistance. The aim of the present study was to investigate the functional significance of *Socs3* by studying mice with heterozygous *Socs3* deficiency.

Results: *Socs3*^{+/-} mice show a greater sensitivity to exogenously administered leptin than wild-type control mice: an enhanced weight loss and an increased hypothalamic leptin receptor signaling were observed. In addition *Socs3*^{+/-} mice are significantly protected against the development of diet-induced weight gain as well as against the associated metabolic complications.

Conclusion: *Socs3* is a molecular mediator of leptin resistance in vivo, suggesting that strategies to lower or inhibit the action of *Socs3* may be of value in the prevention and treatment of human obesity and associated insulin resistance.

This report demonstrates that *Socs3*^{+/-} mice show a greater sensitivity to exogenously administered leptin than wild-type control mice. The leptin receptor is highly expressed in the hypothalamus and belongs to the cytokine-GH-receptor superfamily that activates the Janus kinase-signal transducers and activators of transcription (Jak-Stat) pathway. Potential mechanisms for leptin resistance have been proposed and include defective transport of leptin across the blood-brain barrier, defects in leptin signal transduction and central antagonism of leptin physiological actions.

Interestingly, a second paper published 1 week before the present paper came to comparable conclusions: Mori et al. [2] generated a neural cell-specific *Socs3* conditional knockout mouse using the Cre-loxP system. The conditional knockout mice showed *Socs3* deletion in the hypothalamus and cerebrum but not in other tissues. A conditional knockout approach was used since *Socs3*-deficient mice died during embryonic development as a result of placental defects. Mori et al. [2] investigated the effects of *Socs3* deficiency on leptin-induced Stat3 activation by injecting recombinant leptin into mice and subsequent examination of the hypothalamus by immunoblotting and immunofluorescence staining. Stat3 activation 1 h after leptin stimulation was significantly greater in conditional knockout animals compared to their control littermates, and phosphorylation was sustained for a much longer time. Also in this study the *Socs3*-deficient mice showed a greater weight loss after leptin administration than control mice. *Socs3*-deficient mice showed a reduced appetite and body weight gain during a high-fat diet. In addition, it could be shown that *Socs3* deficiency ameliorates insulin resistance induced by a high-fat diet. *Socs3* inhibits insulin signaling by inducing the degradation of IRS-1 and IRS-2, or by direct binding to the insulin receptor. Therefore, one cannot rule out the possibility that *Socs3* inhibits insulin signaling in the brain and that this influences the susceptibility to diet-induced obesity and peripheral insulin resistance.

These two papers support the possibility that the Stat3-Socs3 system in the brain plays a major role in regulating the amount of body fat. In addition, Socs3 seems to be a potential therapeutic target for the treatment of leptin resistance, type 2 diabetes and obesity.

New hormones

Gender differences of adiponectin levels develop during the progression of puberty and are related to serum androgen levels

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Background: Adiponectin is considered to be an important factor in the pathogenesis of metabolic and cardiovascular diseases. Adiponectin is secreted exclusively by white adipocytes and is abundantly detectable in the circulation. In contrast to most other adipocytokines that increase with excess body fat mass, serum concentrations of adiponectin are decreased in obesity. So far only a few data are available on the development of adiponectin serum concentrations during childhood and adolescence. The aim of this study was therefore to investigate the impact of gender, pubertal development, and obesity on adiponectin levels in children.

Methods: Adiponectin levels were analyzed in two large and well-characterized cohorts of normal weight and obese children covering a wide range of age and body mass indices (BMI).

Results: In lean boys adiponectin levels significantly declined during pubertal development resulting in significantly lower levels in adolescent boys compared with girls (5.6 ± 0.5 vs. 7.1 ± 0.5 mg/l; $p = 0.03$). This decline was inversely related to testosterone ($r = -0.42$; $p < 0.0001$) and dehydroepiandrosterone sulfate ($r = -0.20$; $p = 0.007$). In a stepwise forward multiple regression analysis pubertal stage was the strongest independent predictor of adiponectin, with additional influences of BMI SD score and testosterone. As expected adiponectin levels were decreased in obese children compared with lean controls. In obese children adiponectin levels were significantly associated with the parameters of the metabolic syndrome.

Conclusion: The strong association of adiponectin serum levels with pubertal development, the metabolic syndrome and body fat mass in children indicates epidemiological and pathophysiological relevance of adiponectin already in childhood.

This study adds important information to our understanding of the role of adiponectin in children and adolescents. In addition, it provides reference values for adiponectin in lean and obese children of different age and pubertal stage. The association between pubertal development – apart from the degree of obesity – and circulating adiponectin levels need to be considered when interpreting data from pediatric populations. One major finding of this study was that adiponectin levels decrease in parallel with the progression through puberty in boys, but not in girls. This decline was significantly related to plasma androgen levels. Interestingly a comparable association between plasma leptin and androgen levels in children and adolescents was reported recently [3], indicating that at least leptin, as another specific hormone secreted by adipocytes, seems to have a comparable regulation. It could be shown in *in vitro* experiments using primary human pre-adipocytes and adipocytes that different androgens have a potent suppressive effect on leptin expression in adipocytes possibly being responsible for the marked gender difference which developed during puberty [3]. It would be interesting to investigate whether androgens are also able to directly suppress adiponectin expression and secretion in human adipocytes and to further investigate the possible molecular mechanism behind this effect.

Minireview: Gut peptides regulating satiety

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Background: Gut hormones have been identified as an important mechanism that signal to appetite centers in the brain to reduce food intake after meals. Previous work on cholecystokinin (CCK) and ghrelin have suggested that there is a gut nutrient sensor. It has become increasingly apparent that the gut endocrine system plays an important physiological role in postprandial satiety. Very recently the gut hormones PYY, oxyntomodulin and pancreatic polypeptide (PP), which inhibit appetite, and ghrelin, which stimulates appetite, have been identified. These hormones are active within the plasma range seen in humans and represent a novel approach to the treatment of obesity. In the present review as well as in other reviews [4–6] the present scientific knowledge on the function of these hormones is summarised.

Results: The hypothalamus and the dorsal vagal complex appear to be important CNS regions directly regulating appetite. Receptors for the gut hormones are found within the arcuate nucleus of the hypothalamus. The arcuate nucleus can also be directly influenced by circulating factors because it is partially outside the blood-brain barrier. In the following the main scientific information on selected gut hormones are summarised on the basis of the present review.

Ghrelin – Ghrelin is synthesized in the stomach. Ghrelin levels are up-regulated by fasting. Ghrelin is the endogenous ligand for the GH secretagogue receptor. Ghrelin levels are influenced by nutrients rather than gastric distension: an oral glucose load is able to suppress ghrelin levels whereas water alone is not. The local gut effects of ghrelin comprise stimulation of gastric emptying and an increase in gastric acid secretion. In humans, plasma levels are high in the fasted state and fall after eating. Exogenous ghrelin given *in vivo* leads to an increase in food intake. Ghrelin levels are lower in obese subjects compared with lean, and weight loss in obese results in an increase in ghrelin levels. Interestingly, food intake in obese humans is not able to suppress ghrelin levels. Individuals with Prader-Willi syndrome have extremely elevated ghrelin levels.

Peptide YY (PYY) – The main form of PYY is PYY 3–36. PYY is released into circulation after food intake. Animal studies suggest that circulating PYY 3–36 inhibits appetite by acting directly on the arcuate nucleus via the Y2 receptor to which the hormone has a high affinity. Intravenous administration of PYY 3–36 reduces food intake in obese and in lean individuals. Obese subjects, however, have lower fasting PYY levels and a smaller rise after food intake.

Pancreatic polypeptide (PP) – As PYY PP is an appetite hormone belonging to the NPY family. It is produced in the pancreatic islets. During digestion PP secretion is increased. PP reduces food intake in obese and in lean mice. Patients with Prader-Willi syndrome have low basal and meal-stimulated levels of PP. In these patients and in healthy normal weight individuals, PP administration leads to a sustained reduction in food intake during a free-choice buffet meal.

Oxyntomodulin (Oxm) – Oxm is produced by processing of preproglucagon in the gut and brain and is released after eating. Oxm has an anorectic action and appears to act via a GLP-1-like receptor. In humans intravenous administration of Oxm reduces food intake during a free-choice buffet meal.

GLP-1 – Like Oxm, GLP-1 is produced by processing of the proglucagon gene in the gut and the brain. GLP-1 is released from the gut into circulation after food intake. GLP-1 stimulates insulin release and has specific effects on food intake; whereas in rodents an inhibition of food intake was observed after GLP-1 administration, the role of this hormone in a physiological control of human appetite is not clear. However various analogs of GLP-1 which are in development and which are resistant against the rapid breakdown seen with GLP-1 have been shown to improve glycemic control and, in addition, to reduce body weight.

Some of the hormones have been shown to influence food intake and body weight. The interested reader is referred to several recent reviews on the issue of gut peptides regulating satiety [4–6]. Several new chemicals are being developed by pharmaceutical companies to target receptor systems involved in appetite regulation. The peripheral administration of natural gut hormones as therapeutic agents has the theoretical advantage of targeting only the relevant brain appetite systems without affecting other CNS functions. The administration of the naturally occurring gut hormone might offer a long-term therapeutic approach to weight control without deleterious side effects.

Fast-Food habits, weight gain, and insulin resistance (the CARDIA study): 15-year prospective analysis

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Background: From its origins in the 1950s, fast-food consumption has increased world wide in the last years. Although it seems to be obvious that this development is causally associated with the increased body weights in children and the metabolic adverse effects of obesity, there are no good scientific data to support this assumption.

Methods: The Coronary Artery Risk Development in Young Adults (CARDIA) study is a multicenter, population-based, prospective study of the cardiovascular disease risk factor evolution in a US cohort of young adults. Multiple linear regression models were used to investigate the association of frequency of fast-food visits at baseline and follow-up with 15-year changes in body weight and insulin resistance. 3,031 young adults were involved in this study. For dietary assessment a structured interview was performed.

Result: After controlling for lifestyle factors, fast-food frequency at baseline was directly associated with body weight changes. In addition the changes in fast-food frequency were also associated with changes in body weight. Furthermore these changes were directly associated with insulin resistance as measured by homoeostasis model (HOMA). Individuals visiting fast-food restaurants more than twice a week at baseline and follow-up gained 4.5 kg body weight more than individuals visiting fast-food restaurants less than once a week and had a twofold greater increase in insulin resistance. For white but not for black individuals those with a high frequency of fast-food restaurant visits had fewer years of education, a lower physical activity level and watched more hours of television, consumed more alcohol and had a lower intake of whole grains, fruit and non-starchy vegetables.

Conclusion: Fast-food habits have strong, positive, and independent associations with weight gain and insulin resistance in young black and white adults.

This study demonstrates that fast-food consumption has a strong, positive, and independent association with weight gain and insulin resistance in young people. Fast-food consumption can be linked to adverse health outcomes through plausible mechanisms, and results from other studies support the present findings. In view of the high and increasing rates of fast-food consumption, further research into the effects of the dietary pattern on public health should be given priority. The strength of the present study is the long-term prospective design with a high rate of follow-up over 15 years and the standardized, detailed measurement of dietary practices including the direct assessment of specific fast-food habits. Due to its observational nature, there are of course limitations to this study which do not make it possible to prove causality. The most obvious explanation for the main results is given by the fact that fast-food probably leads to weight gain because of the large portion sizes and the high energy density. Certain fast-foods contain large amounts of partially hydrogenated oils and this class of fatty acids can cause insulin resistance and increase the risk of type 2 diabetes. Fast-food also contains large amounts of highly refined starchy food and added sugar, carbohydrates that have been characterized as high in glycemic index. Modest lifestyle changes including the control of the consumption of fast-food products helps adolescents to control their body weight and to improve insulin resistance as shown in a very recent study of Balagopal et al. [7]. It is not unreasonable to expect health authorities to insist that fast-food outlets restructure their menus.

Sugar-added beverages and adolescent weight change

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Background: In nationally representative samples of US adolescents, intakes of sugar-added beverages, including soda, have increased [8]. This may be partly responsible for the increased prevalence of obesity. The aim of this study was to evaluate the relationship between intakes of sugar-added beverages and the subsequent increase in BMI.

Methods: Participants of the US Growing Up Today Study (prospective cohort study including >10,000 boys and girls) completed questionnaires in 1996, 1997, and 1998. An analysis of BMI changes over two 1-year periods and the beverage intakes corresponding to each BMI change were performed using different models adjusting for confounding factors.

Results: The intake of sugar-added beverages was significantly associated with BMI gains during the corresponding year. Further adjusting the models for total energy intake substantially reduced the estimated effects, which were no longer significant.

Conclusion: Consumption of sugar-added beverages may contribute to weight gain among adolescents, probably due to their contribution to total energy intake. The data suggest that children who reduce their intakes of sugar-added beverages may prevent excessive weight gains.

In addition to the study described above on the influence of fast-food consumption on weight gain by Pereira et al., this study additionally provides an unsurprising but important reminder that the typical diets of industrialized countries is one major influencing factor for the development of obesity. Sugar-added beverages may encourage further energy intake because of their high glycemic index [9]. Especially at younger ages, diets with a high glycemic index program β -cell function leading to increased insulin secretion, which in itself could be a motor for further weight gain. Although this study could establish clear relationships between the intakes of sugar-added beverages and further weight gain, the magnitudes of these estimated effects sound small. A boy consuming 3 servings/day of sugar-added beverages over 10 years is expected to gain 0.9 BMI points more than if he consumed none. Yet, its contribution to insulin resistance and the metabolic syndrome is more important by far. The results of this study support the concept that beverage intakes are a potential target for improving the diets of adolescents. Obesity prevention programs focusing on reducing intakes of sugar-added beverages, along with other behavior modifications such as increasing physical activity and reducing time with TV/videos/computer games, may prevent excessive weight gains. Recently a school-based prevention program, performed as a cluster randomized controlled trial, could in fact show that childhood obesity can be decreased by reducing the consumption of sugar-added beverages [10]. Consequently during the last 12 months several governments have prohibited soft drink vending machines in schools.

Clinical trials, new treatments

Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study

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Background: The cannabinoid-receptor type 1 (CB₁) G-protein-coupled receptor and its endogenous ligands, the endocannabinoids, are involved in the regulation of food intake [11]. In the present study the

effect of rimonabant, a selective CB₁ blocker, was assessed on body weight and cardiovascular risk factors in overweight patients.

Methods: In a randomized, double-blind, placebo-controlled study the effects of 5 and 20 mg rimonabant once daily in addition to a mild hypocaloric diet (600 kcal/day deficit) was investigated on the endpoint weight change from baseline after 1 year. An intention-to-treat analysis was performed.

Results: Patients treated with 5 and 20 mg rimonabant/day lost significantly more weight after 1 year than patients treated with placebo (3.4 ± 5.7 and 6.6 ± 7.2 vs. 1.8 ± 6.4 kg, $p < 0.001$). 20 mg rimonabant/day resulted in significantly greater improvements than placebo in cardiovascular risk factors and factors of the metabolic syndrome.

Conclusion: This study shows that modulating the activity of the endocannabinoid system by blocking its CB₁ receptors holds therapeutic promise as an approach to the treatment of obesity and associated risk factors.

The robust effect of the recreational drug, marijuana (*Cannabis sativa*) on appetite and food intake has been widely known for centuries. The discovery of the cannabinoid receptor type 1 provides a molecular basis for investigating the effect of this popular albeit mainly illegal herbal drug and its constituents. The endogenous cannabinoid system therefore represents a new and promising drug target. This first large, multicenter, randomized, placebo-controlled trial assessed the efficiency and safety of rimonabant in reducing body weight and improving cardiovascular risk factors in overweight patients. Treatment with rimonabant was associated with clinically meaningful weight loss and additional improvement in waist circumference, lipid concentrations, and insulin resistance and had a favorable safety profile. A number of studies show that the endogenous cannabinoid system is able to modulate energy homeostasis via a dual mechanism: cannabinoids are centrally acting orexigenic factors and possess a peripheral lipolytic effect [12]. Very recently, another possible mechanism has been elucidated: Osei-Hyiaman et al. [13] have demonstrated that endocannabinoid activation at the hepatic CB₁ receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. Treatment with a CB₁ agonist reversed this effect [13]. One possible explanation for the potential weight independent effect of rimonabant on cardiovascular risk factors might be related to the observation that it stimulates the expression of adiponectin in fat cells. Therefore improved fat cell function may be postulated as a key peripheral effect of rimonabant leading to body weight reduction and improvement in metabolic parameters.

Treatment of obese adolescents with sibutramine: A randomized, double-blind, controlled study

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Background: Sibutramine has been shown to be an efficacious and safe anti-obesity agent in adults. So far there are only few data on the safety and efficacy of this drug in adolescents.

Methods: In a randomized, double-blind, placebo-controlled trial with 60 adolescents the effect of 10 mg/day sibutramine on body weight was investigated. In addition the patients received dietary and physical activity counseling.

Results: During the 6-month treatment period patients in the sibutramine group lost an average of 10.3 ± 6.6 kg, and patients in the placebo group 2.4 ± 2.5 kg ($p < 0.001$). The adverse effects were mild and no differences in blood pressure or heart rate were noted between the groups.

Conclusion: Sibutramine seems to be an efficient drug to significantly reduce body weight in obese adolescents within a short time period.

This paper shows that sibutramine seems to be an efficient drug to significantly reduce body weight in obese adolescents within a short time period. Pediatricians have so far been reluctant to use pharmaceutical or surgical interventions in childhood obesity. Behavioral therapy is preferred, but does not produce clinically significant weight loss in most patients. Whereas more drastic intervention

cannot be currently recommended, it is time that they are tested in well-designed clinical studies. There is only one study published so far describing the effects of sibutramine plus a structured behavior therapy program in obese adolescents [14]. There are certainly more data, especially long-term data, necessary before conclusions can be made about the indications for the use of sibutramine in specific adolescents. Sibutramine (β -phenethylamine) inhibits the re-uptake of noradrenalin and serotonin. It results in a reduced energy intake and stimulation of the sympathetic nervous system, leading also to an increased thermogenesis. The adverse events were significant for constipation only, which occurred in 40% of sibutramine-treated subjects and in 11% of placebo-treated subjects. In general, sibutramine was well tolerated in the adolescents studied. In contrast to the study of Berkowitz et al. [14], in this study no clinically significant increase in blood pressure or heart rate was observed. Since concerns about heart valves and other cardiac abnormalities have been raised in association with phenfluramine, echocardiographic examinations were also performed which showed no heart modifications. This study is the second showing that, over a short period of time, treatment of obese adolescents with sibutramine seems to be safe and results in significant weight losses. However, on the basis of the data of this study no conclusions can be made about the use of this drug outside clinical protocols. Further long-term data are needed that should be obtained in controlled studies in association with a more intensive behavioral program.

Conjugated linoleic acid supplementation for 1 year reduces body fat mass in healthy overweight humans

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Background: Conjugated linoleic acid is a mixture of linoleic acid isomers with conjugated double bonds. Conjugated linoleic acid has been shown to have beneficial effects on health, including protection against arteriosclerosis, and normalization of impaired glucose tolerance and improvement of hyperinsulinemia.

Methods: In a double-blind, placebo-controlled study 180 obese volunteers were randomly assigned to receive either 4.5 g olive oil (placebo), 4.5 g conjugated linoleic acid-free fatty acids or 4.5 g conjugated linoleic acid-triacylglycerol. DXA-technology was used to assess changes in body composition.

Results: After 12 months of treatment lean body fat mass in the conjugated linoleic acid-triacylglycerol and in the conjugated linoleic acid-free fatty acid groups was 8.7 ± 9.1 and $6.9 \pm 9.1\%$, respectively, lower than that in the placebo group ($p < 0.001$). In addition subjects receiving conjugated linoleic acid-free fatty acid had a $1.8 \pm 4.3\%$ greater lean body fat mass than the subjects receiving placebo ($p = 0.002$).

Conclusion: A conjugated linoleic acid mixture containing *trans*-10, *cis*-12 and *cis*-9, *trans*-11 isomers administered either in the triacylglycerol or free fatty acid form to healthy overweight adults for 1 year results in a significant decrease in body fat mass. Further studies are needed to investigate the metabolic alterations associated with this treatment and to prove its safety.

This is the first clinical study documenting the long-term effects of conjugated linoleic acid supplementation in overweight subjects consuming an ad libitum diet and without specific lifestyle restrictions. The mechanisms by which conjugated linoleic acid decreases body fat mass are not completely understood. Conjugated linoleic acid is known to accumulate in tissues where it is readily metabolized. In vitro and in vivo studies suggested that the ability of conjugated linoleic acid to reduce adipose tissue could be explained by one or more of the following mechanisms: (1) induction of adipocyte apoptosis; (2) reduced accumulation of fatty acids in adipocytes due to an inhibition of lipoprotein lipase and increase in carnitine palmityltransferase; (3) binding to peroxisome proliferator-activated receptor- γ (PPAR γ) present in fat tissue and modification of the signaling cascade to down-regulate the expression of leptin, and (4) prevention of the triacylglycerol accumulation in adipocytes, or modification of the energy expenditure, the metabolic rate, or both.

Although the *cis*-9, *trans*-11 isomer of conjugated linoleic acid has been shown to have adverse effects on insulin resistance [15], the supplementation of a conjugated linoleic acid mixture, as done in the present study, seems to be a promising way of supporting weight control.

Insulin sensitivity among obese children and adolescents, according to degree of weight loss

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Background: Behavioral treatment programs including physical activity and nutrition education and parental education are effective for a specific subgroup of children and adolescents with obesity. The results obtained by such conventional treatment approaches are comparable to those obtained by pharmacological treatments. One of the most severe complications of childhood obesity is a reduced insulin sensitivity which itself is the key factor in the pathophysiology of the metabolic syndrome and the development of type 2 diabetes. Weight loss is the appropriate approach to increase insulin sensitivity and to treat or prevent the metabolic syndrome and its cardiovascular endpoints as well as to prevent type 2 diabetes mellitus. The present study examines the question about how much weight loss is needed to improve insulin sensitivity in obese children and adolescents.

Methods: Insulin sensitivity indices (ISIs) for glucose metabolism and fat metabolism were studied during a 1-year behavioral treatment program for obese children.

Results: When the children were divided into groups according to their changes in body weight it was found that those with a change of BMI-SD-Score (SDS) of more than 0.5 showed a significant improvement of ISIs whereas there were no changes in insulin sensitivity indices in patients who lost less than 0.5 BMI-SDS. Furthermore, it was shown that those subjects who increased their degree of overweight showed a significant decrease in ISI values indicating a further reduction of insulin sensitivity.

Conclusion: Children's failure to achieve weight loss was associated with a decrease in insulin sensitivity after 1 year. More importantly, however, on the basis of the present data it can be expected that reductions in BMI-SDS of 0.5 or more will lead to a significant improvement in insulin sensitivity. The study also shows that comprehensive treatment strategies for childhood obesity are able to reduce a major risk factor for cardiovascular disease.

The 1-year outpatient treatment program for obese children and adolescents developed by the group of Reinehr et al., named the Obeldicks program, is a well-designed structured program aiming at behavioral changes in physical activity and nutrition in both patients and their families. It requires an interdisciplinary team of pediatricians, dieticians, psychologists, and exercise physiologists. Reinehr and co-workers have reported on the evaluation of their program in more than 10 articles published in peer-reviewed journals. Their treatment approach has now become an internationally recognized example for good practice in treating a subgroup of obese children and adolescents who fulfill the prerequisites in participating in this specialized program. It is known from several studies that insulin sensitivity improved quickly when short-term weight reduction is achieved. This is one of the few reports showing that long-term weight loss in obese children results in an improvement of insulin sensitivity. However, the data also show that a significant reduction in body weight is required for this long-term improvement in insulin sensitivity. The study shows once more that increases in body weight in obese children during childhood are associated with decreases in insulin sensitivity.

Atkins and other low-carbohydrate diets: hoax or an effective tool for weight loss?

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Background: Many low-carbohydrate diets have followed the popular diet proposed by Dr. Atkins. The present article gives a summary of current scientific knowledge on low-carbohydrate diets based on a systematic review of known low-carbohydrate diets.

Definitions: The Atkins diet recommends a restricted intake of carbohydrate to initially less than 20 g/day, mainly as salad greens and other non-starchy vegetables. The Atkins diet permits no more than 5–10% of calorie intake from carbohydrate. The unlimited intake of protein and accompanying fat paradoxically seems to promote weight loss.

Results: Based on three randomized trials reporting long-term effects, there is no evidence that low-carbohydrate diets are superior to the energy-restricted low-fat diets. However, the studies provide evidence that a low-carbohydrate diet produces a higher weight loss than energy-restricted low-fat diets during the first 3–6 months. In addition, somewhat surprisingly, greater improvements in some cardiovascular risk factors were seen in people on low-carbohydrate diet.

Conclusions: The mechanisms responsible for weight loss with the low-carbohydrate diet require clarification. There is no clear evidence that Atkins-style diets are better than any others for helping people stay slim, and despite the popularity and apparent success of the Atkins diet, evidence in support of its use lags behind.

The putative mechanisms behind the weight loss of low-carbohydrate diets are as follows. During severe carbohydrate restriction, glycogen stores and associated bound water are depleted. The depletion of glycogen stores produces ketotic acidosis similar to that seen during fasting. Circulating ketones might also be appetite-suppressing, mimicking the anorexia of starvation. In addition, the success of a low-carbohydrate diet might be due to the restriction of a variety of food choices, the monotony and simplicity of the diet could inhibit appetite and food intake. Also, protein induces a stronger satiating effect than fat and carbohydrates, which would decrease ad libitum food intake and body weight. The improvements in some cardiovascular risk factors seen in people on a low-carbohydrate diet is probably not due to the diet itself since studies in epileptic children on a low-carbohydrate diet for seizure control showed an adverse effect on blood lipids that persisted over 2 years [16]. The restricted intake of fruits, vegetables and whole grain bread and cereals is not commensurate with long-term nutritional adequacy and might pose a second-line increased risk of cardiovascular disease and cancer. Also, halitosis, muscle cramps, diarrhea, general weakness, and rashes are more often reported on low-carbohydrate than on low-fat diets.

Bariatric surgery for severely overweight adolescents: concerns and recommendations

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Background: As the prevalence of obesity and obesity-related disease among adolescents in the United States continues to increase, physicians are increasingly faced with the dilemma of determining the best treatment strategies for affected patients. This report offers an approach for the evaluation of adolescent patients' candidacy for bariatric surgery.

Results: In addition to anthropometric measurements and comorbidity assessments, a number of unique factors must be critically assessed among overweight youths. In an effort to reduce the risk of adverse medical and psychosocial outcomes and increase compliance and follow-up monitoring after bariatric surgery, principles of adolescent growth and development, the decisional capacity of the patient, family structure, and barriers to adherence must be considered. Consideration for bariatric surgery is generally warranted only when adolescents have experienced failure of 6 months of organized weight loss attempts and have met certain anthropometric, medical, and psychological criteria. Adolescent candidates for bariatric surgery should be very severely obese (defined by the World Health Organization as a body mass index of 40), have attained a majority of skeletal maturity (generally 13 years of age for girls and 15 years of age for boys), and have comorbidities related to obesity that might be remedied with durable weight loss. Potential candidates for bariatric surgery should be referred to centers with multidisciplinary weight management teams that have expertise in meeting the unique needs of overweight adolescents. Surgery should be performed in institutions that are equipped to meet the tertiary care needs of severely obese patients and to collect long-term data on the clinical outcomes of these patients.

The majority of severely overweight adolescents are resistant to common treatment approaches. If these patients suffer from severe obesity-related comorbidities, new therapeutic approaches are necessary. Bariatric surgery has been known for more than 40 years as an efficient treatment for severe obesity. Recent data from the prospective, controlled Swedish Obese Subject Study, in which a large group of subjects was enrolled, show that the long-term outcome (over 10 years) is beneficial in several aspects. As compared with conventional therapy, bariatric surgery appears to be a viable option for the treatment of severe obesity in adults, resulting in long-term weight loss, improved lifestyle, and amelioration in risk factors [17].

World-wide experience with a surgical approach to childhood obesity is limited. The present review comprises a summary of results reported on the outcome of bariatric surgery in obese adolescents as well as consensus recommendations reached by a group of surgeons and pediatricians specialized in the treatment of childhood obesity. The key issues discussed include patient evaluation and selection, surgical treatment, and long-term follow-up monitoring. The different surgical procedures are summarized. The mechanisms involved are discussed and involve not only reduction of food intake but also alterations in the neuroendocrine control of body weight, potentially through modulation of peptide YY or ghrelin levels.

The 1991 National Institutes of Health Consensus Conference Guidelines [18] suggested the use of adult guidelines in adolescents and younger age groups. We believe that this would overlook the unique metabolic, developmental, and psychological needs of adolescents and could result in the inappropriate use and/or overuse of weight loss surgery for adolescents. However, we doubt that we are at a stage of making recommendations but rather in need of well-designed trials and comprehensive monitoring.

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