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Morbid Obesity in Adolescents

Conservative Treatment and Surgical Approaches

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Preface

Overnutrition, Overweight, and Obesity are the main health problems in industrialized countries worldwide. One of the most striking phenomena is the prevalence in which many young individuals are affected with obesity and its health- and psychological consequences. These health hazards are much more influencing on the general well-being of children and adolescents and their families than most medical practitioners can imagine. Data has been showing that the quality of life in adolescents affected with the burden of obesity can be compared to subjects suffering from cancerous diseases. Moreover, the many morbidly obese young subjects are a group of patients who are affected with very severe problems in regard to metabolism, skeletal health, and skin. They often are unable to take part in sportive activities and tend to be socially isolated with a high probability of becoming depressive. Most of the available conservative treatment procedures are not adequately successful; therefore many centers around the world have commenced with surgical methods in the last decade. It is obvious that these procedures are very drastic and invasive and are accompanied by side effects like nutritional deficiencies, psychological disorders, and, in some cases, consequent surgical interventions. Based on these facts we tried to bring outstanding experts from various fields together and organized a 2-day meeting in Vienna. Our aim for this book was to present the lectures in a comprehensive form, dealing with different aspects of bariatric surgery in adolescent patients from epidemiology, effects on metabolism, accompanying diseases, options for conservative treatments, legal aspects, and the very experiences from international bariatric centers.

We hope that physicians, pediatricians, surgeons, clinical nutritionists, psychologists, and social care workers will receive appropriate and evidence-based information in this rather new field of adolescent medicine. One final goal should be to focus on the importance of efforts to prevent morbid obesity from occurring.

Vienna, Austria — K. Widhalm
Vienna, Austria — G. Prager

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Chapter 1
Paediatric Body Composition Measurement Techniques in Morbidly Obese Patients

Caterina Tosi and Angelo Pietrobelli

1.1 Introduction

Morbid obesity is a serious health problem that occurs also among younger age groups, and it is associated with several co-morbidities (Tian et al. 2011). Surgery is currently the most effective method for achieving significant weight loss in severely obese patients even in adolescents (Jen et al. 2010). One consequence of this situation is that there is now a need for evaluating the body composition both in clinical practice and as part of research (Roche et al. 1996; Heymsfield et al. 2005; Pietrobelli and Heymsfield 2002) to detect the impact of the rapid weight loss incurred with bariatric surgery in growing subjects (Tamboli et al. 2010).

Several techniques are available both in day clinical practice and in research setting, varying in complexity and ease to use (Pietrobelli et al. 2003). All of them make assumptions that may affect its use in different conditions. It is important to underline that a single technique is unlikely to be optimal in all circumstances (Jen et al. 2010; Roche et al. 1996; Heymsfield et al. 2005; Pietrobelli and Heymsfield 2002; Pietrobelli et al. 2003). We need also to underline that adult body composition measurement methods and data may not be directly applicable to paediatric population (Pietrobelli et al. 2008). Another thing that needs to be mentioned is that the in vivo techniques do not measure body composition directly, but rather predict it from measurements of body properties. In this way, all techniques suffer from the two types of error, methodological error when collecting row data and error in the assumptions by which data are converted to the final values (Roche et al. 1996; Heymsfield et al. 2005; Pietrobelli and Heymsfield 2002). The relative magnitude of these errors varies between techniques.

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1.1.1 Background

Body composition analysis methodology divides body mass into components on the basis of differing physical properties. These techniques are used in the study and management of disease states and have been applied to the measurement of physiological changes of the human body in growth and development, the effects of exercise and treatments (Roche et al. 1996; Heymsfield et al. 2005; Pietrobelli and Heymsfield 2002; Tamboli et al. 2010).

Obesity is challenging the body composition measurements due to altered body hydration, difficult to partitioning fat mass (FM) and fat free mass (FFM) and because several methods have less accuracy and precision in this population. Measurements for quantifying total body and regional adiposity and for mapping adipose tissue distribution to evaluate metabolic risk factors both in children and in adults are discussed.

We summarised the advantages and disadvantages of the body composition measurement methods discussed in this chapter having the opportunity that measurements chosen will provide a simple framework to aid decision-making in day-by-day clinical practice.

A range of techniques are available. Some of those producing the most accurate data are the so-called "gold standard" or reference methods, although these techniques have disadvantages of cost and availability (Roche et al. 1996; Pietrobelli and Heymsfield 2002; Pietrobelli et al. 2003; Woodrow 2009). On the other hand, simpler techniques are well tolerated, portable and can be used in day-by-day clinical work, unless that could be less accurate (Roche et al. 1996; Pietrobelli and Heymsfield 2002; Pietrobelli et al. 2003; Woodrow 2009; Wells and Fewtrell 2008; Sweeting 2007). In morbidly obese subjects it is important also to use techniques that allow the assessment of regional, as opposed to whole-body composition (Roche et al. 1996; Woodrow 2009; Wells and Fewtrell 2008; Sweeting 2007).

1.2 Methods to Assess Fat

1.2.1 Density-Based Methods

Densitometry is based on estimating body composition from measurement of total body density (Pietrobelli and Heymsfield 2002; Pietrobelli et al. 2003; Woodrow 2009; Wells and Fewtrell 2006, 2008; Sweeting 2007; Goran 1998; Sopher et al. 2005). The methodology consists in weighing the subject while submerged in a large tank and also outside the tank. The technique is a two-compartment model and is based on the different tissue densities of the FM and FFM compartment of the body. It is based on Archimedes' principle that if the density of an object exceeds that of water, it will sink (Pietrobelli and Heymsfield 2002; Pietrobelli et al. 2003;

Woodrow 2009; Wells and Fewtrell 2006, 2008; Sweeting 2007; Goran 1998; Sopher et al. 2005). It has been crucial as a reference technique in development of the discipline of body composition analysis (Heymsfield et al. 2005). Current limitations for applying densitometry to the obese paediatric population include practical problems (i.e. the technique requires climbing into a large tank of water) and theoretic consideration (i.e. test adherence in obese population is extremely difficult) (Heymsfield et al. 2005; Goran 1998; Sopher et al. 2005).

Air displacement plethysmography measures the volume of air the subject displaces inside an enclosed chamber. Such a device, called the BodPod, is an alternative method for measuring body density. Given the subject's volume and weight, their density can be calculated (Heymsfield et al. 2005; Wells and Fewtrell 2006; Sopher et al. 2005). In obese subjects, reliability of the BodPod is good either the validity (Roche et al. 1996).

1.2.2 Scanning Methods

Computerised tomography (CT) and Magnetic resonance imaging (MRI) can assess not just overall FM, but also its regional distribution. This important point is fundamental to follow the results over time after bariatric surgery (Roche et al. 1996; Pietrobelli and Heymsfield 2002; Sopher et al. 2005). Early accumulation of intra-abdominal adipose tissue in obese subjects is clinically relevant, because there is a high significant relationship with adverse health, including dyslipidaemia, glucose intolerance and cardiovascular disease risk. The only limitation is related to the fact that large individuals cannot fit within field of view (Roche et al. 1996; Sweeting 2007; Sopher et al. 2005).

Dual energy X-ray absorptiometry (DXA) provides whole-body and regional estimates of three main components: bone mineral, FM and FFM. A series of transverse scans, via low-energy X-ray beams, progress centimetre by centimetre across the body and are collected by an external detector. DXA has been shown to be a precise measure of percent body fat (%BF) for children and adolescents (Roche et al. 1996; Sopher et al. 2005), although DXA estimates of FM are influenced by "trunk thickness" with the error increasing as the individual's trunk thickness increases (Roche et al. 1996; Wells and Fewtrell 2006; Sopher et al. 2005). DXA technology relies on several assumptions of tissue constancy that may not always be accurate in particular in morbidly obese adolescents. For example, *R*-values are attenuation ratios that are assumed stable for specific components such as FM and FFM (Roche et al. 1996; Sopher et al. 2005). However, *R*-values measured by DXA for homogeneous material may systematically change as thickness of depth varies (Pietrobelli et al. 1996, 1998). Due to scan problems, half-body scan methodology for %BF, FM, FFM and bone mineral content was found as a valid alternative to full-body analysis in morbidly obese children and adolescents (Breithaupt et al. 2011). Using DXA the effects of surgery on bone mineral density were measured. In adults, was observed a 3 % decrease of total bone mineral

density after 1 year of surgery, with column and pelvis (7.4 % and 10.5 %, respectively) being their main contributors (Carrasco et al. 2009).

Bioelectrical impedance analysis (BIA) is a commonly used method for estimating body composition based on a 2C body composition model (Roche et al. 1996; Pietrobelli and Heymsfield 2002; Tamboli et al. 2010; Sopher et al. 2005). BIA measures the impedance or resistance to a small electrical current as it travels through the body's water pool (Roche et al. 1996; Pietrobelli and Heymsfield 2002; Tamboli et al. 2010; Sopher et al. 2005). Electric currents pass more easily through body fluids in muscle and blood, but encounter resistance when they pass through fat, since it contains little water (Sweeting 2007). In obese subjects BIA is used to indicate whether changes in FFM are in the same direction of weight (Roche et al. 1996; Pietrobelli and Heymsfield 2002; Tamboli et al. 2010; Sweeting 2007; Sopher et al. 2005). Recently Leal and colleagues showed in morbidly obese subjects total body fat along with TBW was related to metabolic and inflammatory profile (Leal et al. 2011). Analysis of the resistance and reactance, components of impedance, at single conventional frequency (50 kHz) provides information about the Extra Cellular Water (ECW) and Intra Cellular Water (ICW) components of Total Body Water. Multiple-frequency BIA techniques utilise the lower penetration of ICW space by low-frequency current to estimate ECW and ICW separately by performing measurements at differing frequencies (Sweeting 2007).

1.2.3 Anthropometric Methods

Skinfold measurements: Subcutaneous fat is estimated by firmly grasping a fold of skin with callipers and raising it, with no muscle included. Single site measurements, e.g. triceps skinfolds are simplest (Roche et al. 1996; Heymsfield et al. 2005; Pietrobelli and Heymsfield 2002; Pietrobelli et al. 2003; Sweeting 2007). This method, useful in normal weight and overweight subjects, is quite difficult to perform in obese subjects due to large thickness and is subsequently not useful at all in morbidly obese subjects.

Waist circumference: Ideally measured using a flexible plastic tape with a sprung handle to ensure reproducible levels of tension. Waist reflects total and abdominal fat levels, and as an indicator of adiposity is not greatly influenced by height (Sweeting 2007). Waist circumference centiles for children have been developed and it is really useful in the follow-up over time after bariatric surgery (McCarthy et al. 2001; Eisenmann 2005; Fernandez et al. 2004).

Body Mass Index (BMI): it is the most frequently used measure of weight in relation to height. However, despite the "universal" use, there are several disadvantages. This simple measurement in paediatric must be adjusted for age and gender and also BMI is not able to disentangle FM from FFM.

1.3 Conclusion

With the increasing popularity of bariatrric surgery as a means of weight loss even in adolescents, it is imperative to understand the impact of weight loss incurred in this procedure. According to the "Inter-disciplinary European guidelines on surgery of severe obesity" in adolescents, bariatric surgery, among other indications, can be considered if the patient has a BMI >40 (or 99.5° percentile for respective age) and at least one co-morbidity (Fried et al. 2007). However, it is fundamental to know the quality of the weight loss, in light of the "obesity paradox". Obesity is associated with an increased all-cause mortality rate. (Troiano et al. 1996). In contrast, the majority of studies show that weight loss is associated with an increased mortality rate (Andreas et al. 1993). Given the above, the degree of health benefit achieved from weight loss is likely dependent on the degree to which the weight is lost as fat and lean mass is preserved (Allison et al. 1999). It is also well known that lean body mass is positively related to body fat; it is fundamental to measure body composition using more sophisticated methods than simply weight and BMI. In fact, BMI is used almost universally in the clinical setting; it might not be a useful measurement. Rather, to calculate the risk posed by obesity, it is better to measure % body fat or FM as well as FFM in order to obtain more useful information than BMI in particular related to the quality of the weight loss (Pietrobelli and Tatò 2005).

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Chapter 2
Insulin Resistance in the Morbidly Obese Adolescent

Ram Weiss

Multiple causes can drive the development of insulin resistance in children and adolescents, such as sedentary behavior, specific dietary elements, and genetic factors, yet the most common cause in this age group is obesity. Obesity is defined in general as an excess adipose tissue. Adipose tissue may be stored in several depots which differ in their localization, anatomical structure, as well as their metabolic profiles. While most fat is accumulated in adipose tissue, some fat may be deposited within and outside of cells in other tissues such as the liver and muscle. In these tissues, lipids may serve as important sources of energy, yet an excess of their intracellular accumulation may have deleterious effects on specific metabolic processes and intracellular signal transduction pathways. Thus, total body fat serves as a crude parameter in the definition of obesity that may be useful in epidemiological studies, yet has limited utility in the characterization of the metabolic phenotype of an obese individual. In order to provide clinical insights into the impact of the amounts of fat in an individual, one must have a precise description of the distribution of fat into specific depots as well as the deposition of fat in various tissues, specifically in insulin-responsive organs.

2.1 Abdominal Fat Depots

The fact that abdominal obesity is associated with adverse clinical outcomes and associated with insulin resistance has been known since the mid previous century. The "apple-shaped" obesity pattern of men (in comparison to "pear-shaped" obesity characteristic of women) corresponds to increased intra-abdominal fat deposition. Lipid can accumulate in the abdominal region within two main depots: the

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subcutaneous depot and the intra-abdominal depot. While each one of these has been associated with adverse clinical outcomes, it seems that their ratio and not necessarily their absolute levels seem even more critical in regard to the development of peripheral insulin resistance. The simple clinical surrogate of abdominal lipid accumulation pattern is an increased waist circumference. Importantly, in severely obese individuals who have obviously an increased waist circumference, this measurement has limited value.

Intra-abdominal fat, known as visceral fat, differs from subcutaneous fat in its vascular supply and drains directly via the portal circulation into the liver. Visceral fat also differs from subcutaneous fat in its molecular profile manifesting as different secretion patterns of adipocytokines and cytokines. Elegant studies by Jensen et al. (Nielsen et al. 2004) revealed that increased visceral fat is associated with increased delivery of free fatty acids (FFAs) to the liver, yet this FFA flux is responsible for only ~20–30 % and splanchnic bed contributes up to 15 % of FFAs reaching the liver. This implies that visceral fat is probably not the source of the majority of systemic circulating FFAs and its postulated effects on insulin resistance of tissues other than the liver cannot be attributed to increased discharge of FFAs. In obese adolescents, increased visceral fat has been shown to be associated with low whole-body insulin sensitivity and an adverse cardiovascular risk factor profile (Weiss et al. 2003a). On the other hand, a lipid partitioning pattern characterized by low visceral fat and increased subcutaneous abdominal fat has been shown to be associated with increased whole-body insulin sensitivity (Weiss et al. 2005). A proposed mechanism by which visceral fat may cause its adverse effects is related to secretion of inflammatory cytokines. When examined in vitro, visceral fat has been shown to secrete increased amounts of inflammatory mediators, including CRP, IL-6, TNF-α, and PAI-1, in comparison to subcutaneous fat (Fain et al. 2004; Shimomura et al. 1996). Similarly, obese individuals with increased visceral adiposity have increased markers of systemic inflammation in comparison to equally obese subjects with increased subcutaneous fat (Tsigos et al. 1999). In a large multiethnic cohort of obese adolescents it has been demonstrated that increasing degree of obesity and lower insulin sensitivity within a given obesity category are both associated with greater levels of CRP (Weiss et al. 2004). Importantly, the observed CRP levels were mostly within the high-normal range and were indicative of chronic "low-grade inflammation" rather than an acute inflammatory process. Increased visceral adiposity has been shown to be related to a greater atherogenic metabolic profile in obese children (Bacha et al. 2003). Visceral fat has also been shown to be related to greater insulin resistance and lower insulin secretory response in obese children and adolescents (Cruz et al. 2002), thus potentially promoting deteriorating glucose metabolism. Adiponectin levels are lower in obese children with increased visceral fat accumulation (Lee et al. 2006), even when the comparison is made between those with similar overall degrees of adipositiy (Lee et al. 2006). The contribution of visceral fat to the typical subclinical chronic inflammation seen in some obese adolescents may thus be the causal link between visceral adiposity and the metabolic syndrome and its related morbidity.

The classic compartment intended for storage of excess energy is subcutaneous fat tissue; furthermore, its lipid storage capacity is the key of trafficking excess calories. Indeed, upper body fat (mainly from the subcutaneous abdominal tissue) is lipolytically more active than lower body fat and contributes the majority of circulating FFAs in the post-absorptive state (Tan et al. 2004; Guo et al. 1999). This observation may explain the adverse metabolic implications of "male apple-pattern obesity", characterized by greater upper body fat, in comparison to "female pear-pattern obesity" which typically involves greater lower body fat. Thus, the contribution of visceral fat to insulin resistance may be related to elements other than FFA discharge and its presence may be only a surrogate of relatively increased upper body fat depots. The subcutaneous layer of adipose tissue has been proposed to act as a "sink," with the capability to accommodate excess energy in the form of triglycerides in the adipocytes and thus prevent the flow of lipid to other less favorable depots (Frayn 2002). In some individuals this protective mechanism may be of limited capacity, causing non-adipose tissues to be exposed to excess concentrations of lipid, potentially leading to ectopic fat deposition, as observed in some subjects. Danforth was the first to propose the hypothesis that inadequate stores of subcutaneous fat result in lipid overflow into visceral fat and non-adipose tissues (Danforth 2000). Some suggest that the abdominal subcutaneous fat depot has two metabolically distinct compartments—deep and superficial. It has been shown in obese adults that excess fat accumulation within the superficial abdominal subcutaneous compartment may have some beneficial protective effects (Golan et al. 2012), yet no such data have been published in obese adolescents.

While absolute measurements of abdominal fat compartments provide important clinical insights, it seems that ratio of the two is the strongest predictor of an adverse metabolic phenotype. Indeed, obese adolescents with a high visceral-to-subcutaneous fat ratio, who are not necessarily more obese than others, have the worst cardiovascular risk profile along with a greater tendency towards impaired glucose metabolism (Taksali et al. 2008). These adolescents manifest not only increased insulin resistance but also more significant dyslipidemia, altered glucose metabolism, and a tendency for greater levels of liver enzymes (suggesting the presence of early steatosis). It has been shown in obese adults that following bariatric surgery, obesity-driven morbidities (such as hypertension and dyslipidemia) revert to normal in patients who have a priori lower visceral-to-subcutaneous fat ratio and that this ratio remains stable in the face of drastic weight loss (Weiss et al. 2009). Looking at this important issue from a different angle, redistribution of fat from the visceral into the abdominal subcutaneous depot would seem to be beneficial. Indeed, a course of thiazolidinedione (rosiglitazone) has been shown to induce such redistribution and lead to improved insulin sensitivity despite an absolute weight gain (Carey et al. 2002). Thus, in the severely obese adolescent, the degree of insulin resistance is highly dependent on patterns of abdominal lipid partitioning (mainly the ratio of visceral to subcutaneous fat) and not necessarily on the absolute degree of obesity or body fat. Indeed, some severely obese adolescents having a low ratio may demonstrate high-normal whole-body insulin sensitivity

while other seemingly "mildly obese" adolescents having a high ratio may have marked insulin resistance.

2.2 Fat Deposition in Insulin-Responsive Tissues

The amount of lipid deposition in insulin-responsive tissues such as the liver and skeletal muscle is relatively small in absolute terms in comparison to the subcutaneous or even the visceral depots. Despite this, the metabolic impact of lipid deposition in these tissues is substantial. Skeletal muscle is the main tissue that governs glucose metabolism in the post-absorptive state into which the majority of digested glucose is supposed to be delivered. This effect is induced mainly by insulin. Increased intramyocellular lipid (IMCL) deposition has been shown to impair the insulin signal transduction pathway and to be associated with peripheral insulin resistance (Shulman 2000). Obese children with altered glucose metabolism have increased deposition of fat in the muscle despite being overall equally obese to their normal glucose-tolerant counterparts (Weiss et al. 2003b) and increased IMCL is clearly associated with lower insulin sensitivity (Sinha et al. 2002). The tendency to accumulate IMCL may be genetically determined, influenced by factors such as ethnic background as well as influenced by diet and activity (Liska et al. 2007). A tendency for increased IMCL deposition predisposes individuals to greater insulin resistance while obesity with low IMCL deposition seems to be more "metabolically benign." Of note, it is not only the amount of fat deposited in muscle that determines its metabolic impact but also its packaging and intracellular localization. This is demonstrated by the "athlete paradox" where endurance athletes have been shown to have IMCL levels reminiscent of obese patients with type 2 diabetes, yet be extremely insulin sensitive (Dubé et al. 2008a). The difference may be in lipid droplet size (smaller in the athletes) and in localization within the vicinity of mitochondria. These observations suggest that muscle lipid content per se is not the major factor that determines insulin sensitivity rather the way lipid is stored and packaged within the cell. Indeed, these observations are further clarified when studying the effects of lifestyle interventions in obese adults. Moderate exercise in elderly obese individuals leads to a slight increase in IMCL, yet muscle oxidative capacity is significantly improved and whole-body insulin sensitivity is increased (Dubé et al. 2008b). Similarly, diet-induced weight loss along with exercise leads to enhancement of the electron transport chain in skeletal muscle implicating either an increased number or improved functionality of existing mitochondria (Menshikova et al. 2005). These observations have important implications for designing interventions for severely obese children and adolescents as they imply that lifestyle modifications can reverse or modify intramyocellular lipid deposition in a favorable way and lead to increased insulin sensitivity even without major weight loss.

Increased hepatic lipid deposition is similarly associated with the majority of the components of the insulin resistance syndrome in children as well as in adults. Increased intra hepatic lipid is associated with levels of visceral fat and seems to be

an important determinant of hepatic and whole-body insulin resistance (Fabbrini et al. 2009a). Moreover, hepatic fat may accumulate as simple steatosis and be mostly reversible, yet may in some cases rapidly progress to steatohepatitis and cirrhosis. Liver steatosis prior to the development of an inflammatory process has been shown to be a reversible process and to respond well to a low calorie diet as well as to pharmacological agents such as thiazolidinediones that induce shifting of fat from to the subcutaneous tissue (Musso et al. 2010). A reduction in transaminase levels (Nobili et al. 2008) and that of liver fat assessed noninvasively using NMR spectroscopy (van der Heijden et al. 2010; Vitola et al. 2009) have been shown in response to weight loss and improvements in insulin sensitivity in children and can potentially serve as surrogates of a reduction in liver lipid deposition.

Whether hepatic fat is accumulated as a result of increased free fatty acid flux from intra-abdominal fat or from accelerated de novo lipogenesis induced by elevated insulin levels (or due to both) is yet undecided. It is clear that hepatic lipid deposition impairs insulin signal transduction within the liver, thus leading to hepatic insulin resistance. This is compensated by a further increase in insulin secretion and might contribute to a vicious cycle of further lipid accumulation in hepatocytes. Importantly, hepatic fat accumulation is strongly associated with a pro-atherogenic lipid profile characterized by increased small LDL and large VLDL particles (D'Adamo et al. 2010a, b). This may be due to the exposure of the lipoprotein synthetic metabolic pathways leading to a "normal" response to "abnormal" insulin levels.

Since intra-abdominal fat accumulation and increased hepatic lipid deposition are tightly associated, it is not straightforward to decipher which of the two is the more dominant driver of the development of insulin resistance. Cali et al. (D'Adamo et al. 2010a, b) endeavored to answer this intriguing question by matching obese children with similar amounts of visceral and intramyocellular fat, yet different amounts of hepatic lipid accumulation. The participants were matched for their degree of obesity, ethnic background, as well as gender. Using a similar approach, Fabbrini et al. (2009b) matched obese adults with similar hepatic fat and different degrees of visceral fat as well as compared those matched for visceral fat and discordant for hepatic fat. Cali et al. performed two-stage euglycemic hyperinsulinemic clamps and demonstrated that suppression of hepatic glucose production during a low-dose insulin infusion is impaired in obese adolescents with increased hepatic fat compared to their counterparts with lower degrees of liver fat. Additionally, during high-dose insulin infusion, those with elevated liver fat show had lower insulin sensitivity compared to those with reduced liver fat. Thus, when matched for intra-abdominal and for intramyocellular lipid deposition, obese adolescents with increased liver fat demonstrate increased hepatic and peripheral insulin resistance independent of the content of other lipid depots. Fabbrini et al. using a similar approach in adults show similar findings regarding increased hepatic and peripheral insulin resistance in subjects with increased liver fat and comparable amounts of visceral fat, yet add an interesting and important observation: using traced palmitate the authors elegantly show a reduced suppression of palmitate rate of appearance during the euglycemic hyperinsulinemic clamp

in subjects with increased hepatic fat and additionally demonstrate an increased VLDL—triglyceride secretion rate delivered from the liver. While Fabbrini concluded that liver fat is the critical determinant of systemic insulin resistance, Cali et al. demonstrate that both visceral and hepatic fat contribute independently to elements of insulin resistance. Of note, the two studies differ in the degree of liver fat of the comparison groups. While the younger patients in the study by Cali et al. had ~1 % liver fat in the low hepatic fat group and ~17 % in the high hepatic fat group, Fabbrini et al. compared a group with ~3 % to a group with 25 % liver fat. On the other hand, Fabbrini also matched two groups with similar liver fat and discordant visceral fat, yet the matching was of subjects with ~13 % liver fat. When performing this comparison, Fabbrini concluded that the groups matched for liver fat and discordant for visceral fat were very comparable metabolically, yet the comparison of two groups with a rather elevated liver fat content a priori may have hidden the independent effects of visceral fat in this comparison. The results of these studies are also supported by the observation that increased hepatic fat is associated with increased insulin resistance assessed in obese children using HOMA-IR (Denzer et al. 2009). Based on these studies, one can conclude that hepatic fat definitely has a major independent role in the development of the insulin resistance phenotype in obese children and adults, yet the independent contribution of other lipid depots such as visceral fat be entirely dismissed.

Taken together, these observations indicate that lipid partitioning is a crucial determinant of the metabolic phenotype of obese individuals of all ages. A favorable partitioning profile (high subcutaneous fat with minimal ectopic deposition in insulin-responsive tissues) is associated with insulin sensitivity and a healthier metabolic profile. A partitioning pattern characterized by relatively lower subcutaneous fat and greater intra-abdominal and ectopic fat deposition in insulin-responsive tissues is associated with an adverse metabolic phenotype. It seems that weight loss does not necessarily lead to an initial loss of fat from the intra-abdominal depot but is rather homogenous in all abdominal compartments, thus maintaining their relative ratios. It is important to indicate that lipid partitioning patterns are also dependent on ethnic background and it is problematic to compare patients from different populations. While the absolute amounts of fat in specific depots such as the intra-abdominal compartment may differ between ethnicities, it seems that their metabolic impact is in the same lines but possibly of different magnitude (Weiss 2007).

The above observations indicate that severe obesity in children as well as in adults are not a unanimous description of a clinical entity. Patterns of lipid deposition as well as packaging and intracellular compartmentalization are the determinants of the metabolic impact of lipid accumulation. This implies that the heaviest individuals are not necessarily those with the worse obesity-driven morbidity. Moreover, when designing clinical interventions for obese children, degree of obesity should probably not be the main selection criterion for participation.

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Chapter 3
Inflammation as a Trigger for Insulin Resistance and Cardiometabolic Disease

Thomas M. Stulnig

3.1 Inflammation and Cardiometabolic Risk

Ten years ago a correlation of body mass index (BMI) with systemic inflammatory markers such as the high-sensitivity C-reactive protein (hsCRP) or interleukin(IL)-6 has been observed. Circulating concentrations of inflammatory markers correlate with fasting insulin levels, an early marker of insulin resistance (Pradhan et al. 2001). Various inflammatory markers also correlate with each other, but hsCRP is currently the most widely applied (Kaptoge et al. 2010). Metabolic syndrome, a compilation of at least three of five factors predisposing to cardiometabolic disease (Alberti et al. 2009), is associated with elevated hsCRP concentrations. Signs of low-grade inflammation are already present in adolescents with some ethnic differences (DeBoer et al. 2011). Moreover, an increasing number of present factors of the metabolic syndrome are associated with elevated inflammatory marker concentrations (Festa et al. 2000). Worsening of glycemia in nondiabetic individuals is particularly related to elevated hsCRP independent of age and reduced adiponectin concentrations (Ong et al. 2011). These data emphasize the important role of inflammatory changes in initiating obesity-related morbidity. Consequently, an elevated risk for type 2 diabetes has been detected in individuals with hsCRP concentrations around the upper limit of normality (Pradhan et al. 2001). In addition, cardiovascular prognosis is significantly worse in individuals with elevated inflammatory marker concentrations independently of LDL cholesterol or presence of metabolic syndrome (Ridker et al. 2002). Based on such data hsCRP concentrations of 3 mg/l or more are applied to define a significantly increased risk for metabolic and cardiovascular disease.

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In obesity, systemic inflammation originates from the adipose tissue but is also found in liver, the vascular wall, pancreatic islets, and muscle. Not all adipose tissue is equal with regard to inflammatory alterations, since visceral adipose tissue in particular is prone to inflammation (Fain et al. 2004). Adipose tissue is recognized as an endocrine organ secreting a huge diversity of mediator molecules with local (auto- and paracrine) and remote (endocrine) sites of action (Zeyda and Stulnig 2009). Most adipokines are inflammatory by nature and interfere with insulin action. Inflammatory mediators secreted from visceral adipose tissue reach the liver in high concentrations via the portal vein rather than being diluted in the circulation as are those derived from subcutaneous adipose tissue. Since the liver is a key target organ of insulin action, inflammatory cytokines from visceral adipose tissue directly impact hepatic insulin sensitivity and metabolic regulation. Moreover, inflammation in visceral but not subcutaneous adipose tissue also induces inflammation in the liver (Cancello et al. 2006). The crucial role of inflammation in visceral adipose tissue inflammation for cardiometabolic risk is also indicated by experiments showing that inflamed visceral but not subcutaneous adipose tissue induces atherosclerotic lesions in lean hyperlipidemic mice (Öhman et al. 2008). Hence visceral adipose tissue, which is generally enlarged in metabolic syndrome and known for provoking insulin resistance, is also a major factor in low-grade chronic inflammation and its poor consequences.

In conclusion, inflammatory adipokines not only provoke local inflammation of the adipose tissue but also lead to inflammatory changes in liver followed by hepatic insulin resistance, and via the circulation to systemic insulin resistance and atherogenesis, the basis of cardiometabolic disease.

3.2 Key Players of Adipose Tissue Inflammation

Adipose tissue enlargement in obesity leads to adipocyte hypertrophy that is associated with poor metabolic function. Endoplasmic reticulum, mitochondrial and oxidative stress, as well as hypoxia have been suggested as primary cause for adipocytes to secrete inflammatory adipokines. Chemokines attract inflammatory cells, predominantly macrophages and T lymphocytes. In a recent clinical study with morbidly obese subjects we have previously shown that expression of several monocyte chemoattractant proteins is elevated in visceral and subcutaneous adipose tissue compared to lean and overweight controls (Huber et al. 2008). In this study the chemokine CCL5 (RANTES), as well as its receptors (CCR1, CCR3, CCR5), was highly expressed in obesity providing a reasonable basis for elevated CCL5 plasma concentrations. Moreover, CCL5 expression was correlated with measures of insulin resistance independent of visceral obesity measured by waist circumference (Huber et al. 2008). These data indicate the importance of inflammatory cells in adipose tissue for metabolic deterioration in obese individuals.

Macrophages recruited to adipose tissue may differ in their phenotype being either more inflammatory (M1) or regulatory (M2) by nature. We have shown that

human adipose tissue macrophages constitute a particular macrophage type being of an anti-inflammatory M2 phenotype by surface marker expression but secrete large amounts of inflammatory cytokines similar to M1 macrophages (Zeyda et al. 2007; Zeyda and Stulnig 2007). Recently, we have refined the picture of macrophages infiltrating murine adipose tissue by dividing them into presumably resident macrophages secreting chemokines and different types of highly inflammatory macrophages that are attracted by expression of fitting chemokine receptors (Zeyda et al. 2010).

The number of known adipokines is steadily increasing. While adiponectin and leptin are specifically expressed in adipose tissue and improve insulin sensitivity, a vast number of adipokines are inflammatory and may be produced in other inflamed tissues as well. By activating inflammatory signaling pathways such as c-jun N-terminal kinase and nuclear factor κ-B, adipokines interfere with insulin action at a molecular level. Hence counteracting inflammatory key pathways and molecules in obese adipose tissue could repress adipose tissue inflammation and hence improve insulin sensitivity and reduce cardiometabolic risk.

3.3 Anti-inflammatory Therapy for Diabetes and Obesity?

A number of interventions in the treatment of obesity and insulin resistance reduce circulating inflammatory markers (Shoelson et al. 2007). Therapeutic lifestyle changes with weight loss in postmenopausal women lead to a reduction of circulating CRP, IL-6, and serum amyloid A (Ryan and Nicklas 2004). Similar changes were found after high-fiber low-fat diet and exercise or intensive physical training (Oberbach et al. 2006; Roberts et al. 2006). Reductions in inflammatory and endothelial markers were observed after bariatric surgery as well (Kopp et al. 2005; Vazquez et al. 2005; Schernthaner et al. 2006). But also insulin sensitizers such as thiazolidinediones and metformin lead to reductions in inflammatory markers (Shoelson et al. 2007). Beyond proposed direct anti-inflammatory actions, e.g., thiazolidinediones activating PPARγ, insulin sensitizers simply disrupt the vicious circle of inhibited insulin action that promotes adipocyte dysfunction followed by cellular stress and advanced inflammatory alterations.

Conversely, a number of direct anti-inflammatory interventions are currently tested for their ability to improve insulin sensitivity and/or prevent cardiometabolic disease (Goldfine et al. 2011). In the TINSAL-T2D study, salsalate, a non-esterifed salicylate derivative, was tested in high dosages (Goldfine et al. 2010). While salicylates are known to interfere with eicosanoid synthesis, they directly inhibit the inflammatory nuclear factor κ-B pathway when given in high concentrations (Kopp and Ghosh 1994). Actually, salicylates were suggested for diabetes treatment more than a century ago (Ebstein 1876; Williamson 1901). Salsalate has a more favorable profile of side effects compared to acetylated salicylates and can be given in dosages of up to 4 g/day as done in the TINSAL-T2D study. Salsalate significantly reduced HbA1c, fasting glycemia, and serum triglyceride

concentrations in the TINSAL-T2D study (Goldfine et al. 2010). In addition, plasma concentrations of the insulin-sensitizing adiponectin were elevated by the treatment. Improved insulin secretion and reduced insulin clearance appeared to have contributed to salsalate's beneficial effects. In addition, endothelial function was improved by salsalate treatment. These results emphasize that anti-inflammatory treatments could successfully improve metabolic and cardiovascular risk in obese individuals.

Our own investigations in obese mice have shown that long-chain n-3 polyunsaturated fatty acids (PUFA), i.e., eicosapentaenoic and docosahexaenoic acid, significantly reduce high-fat diet-induced adipose tissue inflammation and tissue remodeling presumably by interfering with eicosanoid production (Todoric et al. 2006; Huber et al. 2007). We are currently completing a clinical trial with n-3 PUFA treatment in morbidly obese subjects looking on adipose tissue inflammation in which preliminary analyses indicate that the same is true in humans. While the cardioprotective effect of fish oil-derived n-3 PUFA is well documented, these fatty acids could also exert beneficial metabolic functions beyond lowering triglyceride levels. Hence, dietary fat quality is a major factor contributing to inflammatory alterations in obesity and cardiovascular disease.

Recently, we and other have identified osteopontin as a crucial molecule in obesity-induced inflammation and insulin resistance (Nomiyama et al. 2007; Kiefer et al. 2010, 2011). Osteopontin is highly upregulated in obesity in murine and human adipose tissue and increased plasma concentrations are found in obesity as well. We have shown that osteopontin not only activates adipose tissue macrophages, but also adipocytes inhibit insulin responsiveness in this metabolically highly relevant cell type (Zeyda et al. 2011). Osteopontin deficiency renders obese mice more insulin sensitive compared to wild-type controls (Kiefer et al. 2011). Moreover, we have shown that neutralizing osteopontin action in obese mice by means of specific antibodies results in reduced inflammation and improved insulin sensitivity. Since published data point to a significant role of osteopontin in atherogenesis, osteopontin could be an interesting target to treat type 2 diabetes and reduce cardiovascular risk by an anti-inflammatory treatment strategy.

Low-grade chronic inflammation is a critical basis for the development of type 2 diabetes and cardiovascular disease. Based on available data we can now develop and test anti-inflammatory strategies for preventive and therapeutic purposes. A large scientific program headed by the author has recently been established at the Medical University of Vienna to design and evaluate anti-inflammatory immunotherapies for the prevention and treatment of cardiometabolic disease. It is my hope that such anti-inflammatory endeavors will bring forth not only medical progress but first and foremost clinical benefit to the rapidly increasing obese population at high risk for cardiometabolic disease.

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Chapter 4
Inpatient Lifestyle Interventions to Treat Childhood Obesity

Wolfgang Siegfried and Thomas Reinehr

Beyond surgical and pharmacological therapies, there are several forms of lifestyle interventions in the treatment of childhood obesity. These are of great relevance as they focus on changing the behavior of the children and thus addressing an important key feature in the pathway of the development of obesity. Even in severe cases of childhood obesity, this strategy has the potential to be effective. However, studies are needed to clarify the potential predictors for failing or succeeding by participating in such programs to finally know in which individuals more intensive strategies (e.g., surgery) are necessary.

Lifestyle interventions may be performed in an outpatient or an inpatient setting, e.g., residential or weight loss camps, or by the combination of both. In a recent review the effectiveness of those programs was investigated. The average decrease in percent overweight within inpatient treatment across 11 studies was 23.9 % from pre- to post-intervention and 20.6 % from pre-intervention to a follow-up, whereas the effect on percent overweight was 8.5 % and 8.9 % for outpatient programs, respectively (Kelly and Kirschenbaum 2011). Within the evaluation of obesity treatment in children and adolescents study (EvAKuJ study) the short- and long-term effects of different German childhood obesity programs were assessed (Hoffmeister et al. 2011). The authors reported that five out of 48 programs included took place in an inpatient setting (875 patients), whereas all others were carried out in an outpatient setting (1,041 patients). Children participating in inpatient programs achieved a mean reduction in BMI-SDS of −0.36 during the treatment and of −0.17 during the observational follow-up 1–2 years after termination of the treatment, whereas this was −0.18 and −0.21 for outpatient programs,

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respectively (Hoffmeister et al. 2011). In summary, the results of inpatient versus outpatient programs are equivocal especially regarding long-term effectiveness.

These results emphasize that inpatient treatment might be the most effective lifestyle intervention strategy for children to lose body weight in the short term. However, it has to be noted that there is a need for intervention studies with considerably longer duration of follow-up to show the long-term effectiveness of these programs.

In the following, an inpatient program of the rehabilitation clinic "Klinik Schönsicht" in the south of Germany will be presented to show exemplarily the structure of an inpatient lifestyle intervention. Results on the short-, middle-, and long-term effects of this program should illustrate the drawbacks and opportunities of inpatient lifestyle interventions. Furthermore four individual cases of obese children, who have been successfully treated within this program, are reported.

4.1 Lifestyle Intervention Program at the "Klinik Schönsicht"

The "Klinik Schönsicht" is primarily focused on inpatient treatment for childhood overweight and obesity. The duration of the stay depends on health insurance allowance and the severity of obesity. Typically the children are referred to the clinic for 4 weeks and in case of severe obesity or comorbidities they have the opportunity to extend the program. The standardized multimodal program focuses on a calorie-restricted balanced diet, an increase in physical activity, and behavioral counseling. It is conducted by an interdisciplinary team of pediatricians, exercise physiologists, dieticians, psychologists, and pedagogues according to German guidelines for inpatient weight loss programs (AGA, Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter) (Recommendations 2008).

The physical exercise program consists of 10 h structured physical activity per week (therapeutic sports, swimming, group sports, postural training, hiking) and 6 h nonstructured physical activity per week, which includes "fun walks" to the town or various excursions.

The children are offered an optimized balanced diet prepared according to current guidelines (30 %, 15 %, and 55 % of the total energy content from fat, proteins, and carbohydrates, respectively), with an allowed energy intake of 1,250–1,800 kcal/day, depending on height and sex (Kersting et al. 2005).

Additionally, children have six sessions of healthy behavior training per week, which includes lessons on physical activity, energy balance, and physical health, on healthy shopping, cooking, and eating, and on improving social competence based on cognitive-behavioral theory (see Table 4.1).

The parents are only intermittently involved in the inpatient program. Usually at the start and/or the end of the inpatient treatment they receive background information on obesity and advice about how to best support their child. They also

Table 4.1 Various components of the healthy behavior training within the treatment program

Component	Description and aims
Physical education	Improve knowledge on energy balance, physiological effects of physical activity, and measures of self-control → Support adherence to physical activity recommendations
Medical education	Improve knowledge on what is a healthy body weight and medical consequences of overweight and obesity → Support motivation for achieving a healthy body weight and promote realistic goal setting
Lessons on healthy nutrition, cooking, and grocery shopping	• Learn to choose the appropriate (amount of) food • Learn more about healthy shopping, e.g., to read packaging labels correctly • Experience that cooking can be a creative activity and a positive group experience → Enable the children to buy and prepare healthy food for themselves
Psychotherapy	• Development of rules for healthy eating behavior • Learn to recognize signs of hunger and satiety • Learn to enjoy food • Develop motivation for participating in regular physical activity • Learn to cope with difficult situations → Improvement of self-esteem and body perception → Prevention of relapse
Social competence	• Learn to recognize signs of hunger and satiety • Learn to enjoy food • Develop motivation for participating in regular physical activity • Learn to cope with difficult situations → Improvement of self-esteem and body perception → Prevention of relapse

receive some handouts on healthy living for instance with respect to physical activity, nutrition, and media consumption and are advised to organize outpatient support for their child.

4.2 Health Benefits of the Inpatient Lifestyle Program

Every year, about 300 children took part in this inpatient lifestyle program. To evaluate the short-, middle-, and long-term effects of the program, anthropometric data, cardiometabolic risk factors, data on physical activity, and eating behavior of the children were collected and analyzed.

First results from 957 children have shown that all children who completed the therapy (more than 3 weeks of therapy duration) showed a distinct weight loss. The mean BMI was reduced from 33.6 ± 6.1 kg/m^2 to 30.0 ± 5.3 kg/m^2 ($p < 0.001$).

Two years after the start of the therapy, follow-up data of over 50 % of the children could be analyzed ($n = 295$). More than one-third of these children succeeded in the long-term weight loss after their stay at the clinic: Twenty one percent of the children reduced their BMI-SDS by >0.5. Sixteen percent showed a BMI-SDS reduction of 0.2–0.5 and 17 % a reduction of 0–0.2. Eight percent of the children maintained their BMI-SDS and 38 % of the children showed a further increase of BMI-SDS compared to baseline levels.

Even 5 years after therapy start more than one-third of the examined children ($n = 66$) showed a long-term weight loss success: Twenty-four percent of the children showed a BMI-SDS reduction of >0.5 and 9 % had a BMI-SDS reduction between 0.2 and 0.5. However, 55 % of the examined children showed an increase in BMI-SDS compared to the values at the start of the therapy. Even though, these are the first results of only a small number of children, these data indicated that an inpatient lifestyle therapy can be effective even in the long term.

Beyond targeting a successful weight loss, another important aim of obesity therapies is to achieve sustainable lifestyle changes. According to estimations of the WHO, 60 % of the worldwide population is physically inactive. Several studies have shown that physical inactivity and a low physical fitness status are associated with a higher risk for hypertension, stroke (Goldstein et al. 2010), and type 2 diabetes (Colberg et al. 2010), independent of overweight and obesity. The results of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) have shown that only 28 % of boys and 17 % of girls in Germany reach the current recommendations of being physically active equal or more than 60 min/day. Low levels of physical activity are particularly prevalent in girls, in overweight children, as well as in children with a low socioeconomic status or ethnic background (Lampert et al. 2007). At the start of the therapy, the children reported to be physically active on 2.8 ± 2.2 days (≥60 min/day) per week. Positive lifestyle changes with increased physical activity levels ($p = 0.005$) and improved eating behavior ($p = 0.002$) could be observed 6 months after the start of the therapy. However, 5 years later no long-term improvements in a small group of analyzed children ($n = 66$) were found.

Another important health outcome, which has to be considered in the evaluation of weight loss programs, is the health-related quality of life. For example, the KINDL Total Score (scaled from 0 to 100 points) could be improved from the start of the program at the "Klinik Schönsicht" to 2 years later from 65.9 ± 12.4 to 68.6 ± 13.8 points ($p < 0.001$).

In summary, this therapy program has the potential to sustainably improve body weight, quality of life, and behavioral factors. However, it needs to be further elucidated which predictors may have a crucial influence on the success of obesity programs to finally find the most efficient strategy.

Case 1. A 12-year-old boy participated at the weight loss program for 4 weeks in June 2006. At his arrival, he had a body weight and height of 76 kg and 158 cm (BMI: 30.6 kg/m^2; BMI-SDS: 2.5). During the program his body weight decreased by 7 kg, so that he had a BMI of 27.5 kg/m^2 and a BMI-SDS of 2.1 at the day of

discharge. He succeeded to further decrease his BMI at all follow-up dates (6 months, 1 year, and 2 years). Two years after his stay at the clinic he had a BMI of 24.1 kg/m^2 and a BMI-SDS of 1.7. Within this period, he increased the regular physical activity per day (≥60 min) from 3 days to 4 days/week and he became an active member of a judo club. Furthermore he changed his dietary behavior sustainably, so that he was able to maintain his body weight without any professional interventions.

Case 2. A 17-year-old girl participated at the weight loss program for 8 weeks in 2008. At the day of her arrival, she had a body weight and height of 135 kg and 181 cm (BMI: 41.2 kg/m^2; BMI-SDS: 3.8). During the program her body weight decreased by 12 kg, so that she had a BMI of 37.6 kg/m^2 and a BMI-SDS of 3.4 at the day of discharge. Six months after the start of the therapy she had a BMI of 34.2 kg/m^2, whereas this was 35.5 kg/m^2 and 34.0 kg/m^2 at the 1- and 2-year follow-up date. She increased her regular physical activity (≥60 min/day) from none to three times per week. She frequently did spinning and fitness courses at a gym close to her home. Within the first year after the stay in the clinic, she dieted over 4 months by herself.

Case 3. A 12-year-old boy started the inpatient therapy with a BMI of 33.6 kg/m^2. He reduced his weight from 76.6 to 67.6 kg (BMI 29.2 kg/m^2) during the 6-week inpatient therapy. Six months later, he reached a slight further decrease (28.4 kg/m^2). After this first success, he had a severe relapse with an excessive weight gain (37.6 kg/m^2) and considerable mental stress. A further stay at the rehab clinic and the assistance of a personal trainer at home caused a real lifestyle change with distinct weight loss over a longer period.

Case 4. A 10-year-old boy reduced his BMI from 24 kg/m^2 to 22 kg/m^2 during a stay at the rehab clinic. Eight years later he returned to the clinic with a body weight of 285 kg and a BMI of 68.5 kg/m^2. Within 5 months he reduced his body weight by 90 kg (BMI 46.8 kg/m^2). As he struggled to simply walk upstairs at the start of the therapy, he became able to hike walk a distance of 2.5 km with an altitude difference of 200 m in only 20 min within a few weeks. After his participation at the weigh loss program, he further reduced his body weight by 65 kg (BMI 31.0) within 1 year. To tighten his skin, he needed five plastic surgeries. After 220 unsuccessful applications for employment, he found a job and finally he became a very successful self-employed person. He maintained his body weight since 40 years.

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Chapter 5
Conservative Treatment for Morbidly Obese Adolescents: The German Experience

Andreas van Egmond-Fröhlich

5.1 Introduction

Before addressing morbid obesity in Germany, I would like to introduce the German Obesity Working Group in Childhood and Adolescence (AGA) as this organization is closely linked to "the German experience":

The AGA was founded in 1998. It is the largest working group of the German Obesity Society Organization with over 500 members. It has developed evidence-based guidelines for the treatment of obesity on the highest level (Wabitsch and Moss 2009) and advances research [e.g., the EvAKuJ study (Hoffmeister et al. 2011)]. The AGA also certifies obesity trainers, treatment facilities, and trainer academies, and it supports the Documentation/Benchmarking for Obesity Management system (APV) with 177 participating treatment centers in Germany and Austria as of March 2011. This has led to an expanding network of in- and outpatient treatment centers that participate in quality assurance measures of APV. As of November 2012, the APV database contained data on 81,819 patients from 189 specialized pediatric obesity institutions in Germany (Gröber-Grätz et al. 2013).

These efforts at quality assurance also facilitate the financing of obesity treatment through social insurance (e.g., health insurance). For this purpose a consensus statement for patient education programs for children and adolescents with obesity was reached with the active involvement of the German Ministry of Health between AGA and parent organizations of health insurance in 2004 (Bohler et al. 2004).

The AGA has issued a chapter on extreme obesity as part of the level 2 guidelines (Moß et al. 2011) that may be summarized as follows:

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Comorbidities are much more prevalent in extremely obese adolescents than those with lesser degrees of severity:

- Somatic: For example, metabolic syndrome, endocrinological, respiratory, and orthopedic complications.
- Psychological/Psychiatric: For example, impaired self-image, eating disorders, attention-deficit disorder, affective disorders, and electronic media abuse (Lampert et al. 2007).
- Social: For example, abuse, mobbing, social phobias, and school absenteeism.

This places a special burden on treatment facilities with regard to diagnostic and therapeutic capabilities and effort.

Successful therapy thus must involve a multi-professional team including physicians, psychologists, clinical dieticians, and exercise physiologists/therapists. Different approaches are in use in Germany depending on need and local availability:

- Long-term interdisciplinary outpatient treatment.
- Which may be preceded by or include a phase of inpatient rehabilitation.
- Selected patients may require long-term residential care including academic or professional training.
- As indicated, preceding or concomitant psychotherapeutic or psychiatric treatment and/or social work.

Also, centers treating morbidly obese adolescents should be knowledgeable regarding the indications and contraindications for medical and bariatric surgical treatment options.

The risk for (and therefore cost of) major metabolic comorbidities of obesity appears to rise exponentially based on body mass index (BMI) (James et al. 2004). This is supported by the not representative and therefore preliminary data from APV. Based on data from 98 centers, from a subgroup of children and adolescents with a BMI above the 99.5th AGA BMI percentile ($N = 7{,}427$ with measured data, comprising 37.2 % of all APV patients), 56 % had arterial hypertension, 15 % had subnormal HDL cholesterol, 17 % had hypertriglyceridemia, and 8 % had impaired glucose tolerance. There was also a significant association between severity and prevalence of risk factors/comorbidity (I'Allemand et al. 2008) and low HDL cholesterol. Hypertriglyceridemia is even more prevalent, with 26 % and 20 % respectively of patients with a BMI > 45 kg/m^2 (Gröber-Grätz et al. in press). This means that morbidly obese adolescents are at a very high risk of acquiring chronic illnesses and additional risk factors for cardiovascular disease. Aside from suffering from morbid obesity, this also makes them costly to the healthcare system and threatens their productive contribution to society in the long term. Preventing or treating morbid obesity may thus be intensive and lengthy and therefore costly, yet still make sense from a cost-effectiveness perspective.

In contrast to most other countries, inpatient rehabilitation plays an important part in the management of obese adolescents in Germany. In total, 6,311 patients, mostly adolescents, were treated as inpatients for obesity with comorbidity or additional risk factors in Germany in 2007. The majority of the inpatients were extremely obese (van

Egmond-Fröhlich et al. 2006, 2013) with a BMI > 99.5th AGA BMI percentile and based on APV data. 79 % of the 2,734 children and adolescents with a BMI > 40 kg/m^2 were treated as inpatients. Inpatient treatment is financed by both retirement and health insurance. The duration of treatment is usually 4–6 weeks, but this may be extended in severe cases. Treatment is performed by an interdisciplinary team of pediatricians, psychologists, dieticians, exercise therapists, and pedagogues. It consists of dietary and exercise therapy, CBT-based patient education, and psychological treatment as needed. Inpatient rehabilitation goes beyond psycho-education as the behavior change is facilitated by immersion in a healthy lifestyle.

There is currently no published data on the prevalence, treatment status, or conservative treatment success rates of morbidly obese adolescents in Germany.

The German-wide cross-sectional and longitudinal documentation project on extreme obesity in childhood by the German Surveillance Unit for Rare Pediatric Disorders (ESPED) in cooperation with the German Obesity Working Group in Childhood and Adolescence (AGA) has just recently been started. A publication on extreme obesity in children and adolescents based on the APV data is currently in press (Gröber-Grätz et al. in press).

Unfortunately, patients, families, bariatric surgeons, and even health insurance companies are increasingly pressing for the (quick and easy?) surgical option. Evidence-based decisions regarding conservative versus bariatric surgical treatment options for morbidly obese adolescents have to be made today. This was the reason the EAROC meeting has addressed this important issue.

Fortunately, three multicenter German observational in- and outpatient treatment studies that included morbidly obese patients have been recently finished (Hoffmeister et al. 2011; van Egmond-Fröhlich et al. 2006, 2013). This created the opportunity to estimate and compare the success rates of conservative treatment in morbidly and non-morbidly obese adolescents.

Before we can thus reanalyze the data from these studies, two fundamental issues have to be addressed: first, the definition of morbid obesity in adolescents and, second, the definition of treatment success.

5.2 Methods

5.2.1 Definition of Morbid Obesity

There is currently no international consensus regarding the definition of morbid obesity in adolescents. As an indication for bariatric surgery in adolescents, Pratt et al. (2009) used obesity grade III BMI > 40 kg/m^2 (or BMI > 35 kg/m^2 with significant comorbidity like type 2 diabetes mellitus, moderate to severe obstructive sleep apnea, severe or progressive nonalcoholic steatohepatitis, or pseudotumor cerebri). Similar criteria have been proposed in Germany (Blüher et al. 2011). The German Obesity Working Group in Childhood and Adolescence (AGA) currently still defines extreme obesity by a BMI > p99.5 based on the AGA BMI reference

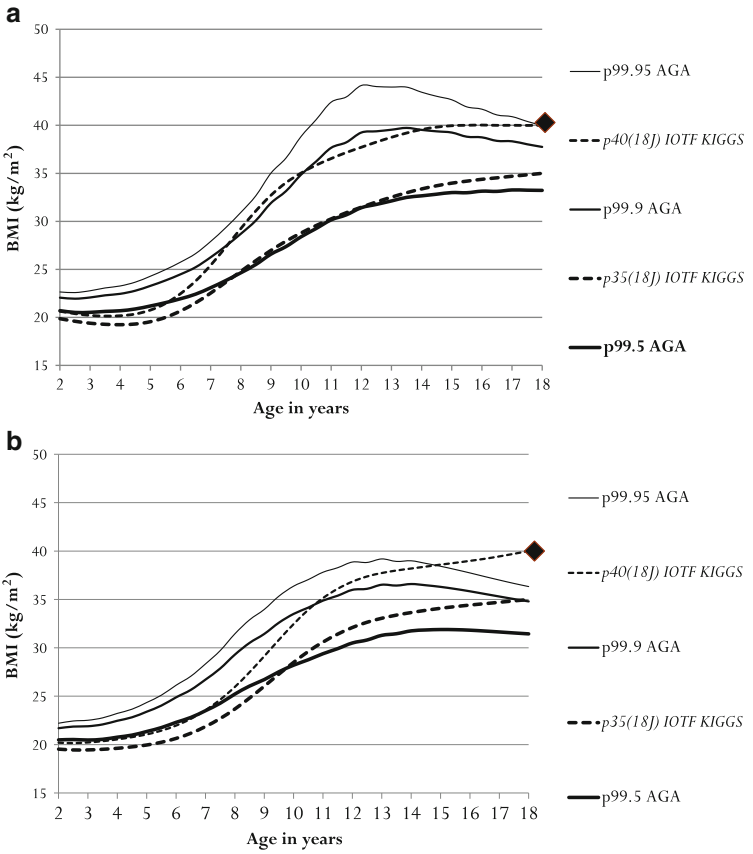

Fig. 5.1 This graph shows the BMI percentiles p99.5 and p99.9 for boys (**a**) and girls (**b**) used to define extreme obesity based on the AGA BMI reference (*continuous lines*). As shown extreme percentiles (even more obvious for p99.95) show a paradoxical decline during adolescence. On the other hand the percentiles based on the more recent German Health Interview and Examination Survey for Children and Adolescents (KiGGS) and derived by back-extrapolation from the BMI values of 40 kg/m^2 and 35 kg/m^2 at 18 years that correspond to the cutoffs for III and II obesity in adults and are in *line* with the IOTF recommendation show a montonous ascending course (*dashed lines*)

(Kromeyer-Hauschild et al. 2001) while the recently started documentation project on extreme obesity in childhood by the German Surveillance Unit for Rare Pediatric Disorders (ESPED) in cooperation with AGA uses a more stringent BMI cutoff (>p99.9). The AGA BMI percentiles show anomalous behavior in adolescence at very high percentiles (see Fig. 5.1a, b). Similar problems with the reliability of extreme BMI percentiles derived by the LMS method have been previously reported with the CDC 2000 BMI reference (Woo 2009; Flegal et al. 2009).

In the current analysis, the IOTF (Cole et al. 2000) method of back extrapolation based on the adult grade III cutoff of a BMI > 40 kg/m^2 was used. The BMI reference of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) (Kurth and Schaffrath Rosario 2007) was selected as a

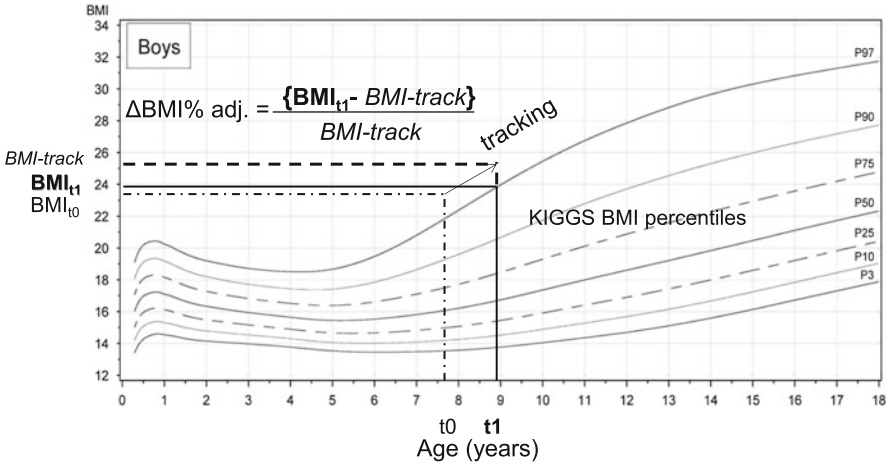

Fig. 5.2 This figure illustrates the method of age-adjusted percent BMI reduction. At baseline (t0) BMI-SDS is calculated based on KIGGS reference. At follow-up (t1) the tracking BMI is calculated from this BMI-SDS. The adjusted percent BMI change is then calculated from the difference of tracking BMI and actual follow-up BMI. This difference is expressed as a percentage of the tracking BMI

basis because of the above-mentioned problems with the AGA BMI reference for morbidly obese adolescents. Our cutoff is in effect similar to BMI p99.9 based on the AGA reference, but it is superior as it shows the expected monotonical increase and is by definition continuously merging into the adult definition at 18 years. It is also marginally superior to a definition of BMI > 40 kg/m^2 as it takes the age dependence of BMI during adolescence, especially in girls, into account.

5.2.2 *Definition of Treatment Success*

There is currently no international consensus regarding the definition of success of obesity treatment. The formerly proposed percentage of patients that achieve normal weight (or overweight) is clearly unjust to patients with more severe obesity at outset. The adult definition of percent change of BMI has its drawback in pediatrics, especially when looking at long-term success as BMI is age dependent. Using the change in percent of being overweight Δ(BMI/BMIp50 * 100) in effect employs the 50th BMI percentile to adjust for the age dependence of BMI, but it overestimates the treatment effect in more severely obese patients (compared to percentage BMI change). Using the change of BMI-SDS score (calculated by the LMS method of Cole) also solves the problem of age dependence, but as the BMI distribution is skewed it puts more severely obese patients at a disadvantage. We therefore used the innovative method of age-adjusted percent BMI change. As illustrated in Fig. 5.2, this method uses the tracking BMI to calculate an estimate for the spontaneous course of BMI during follow-up without treatment and then compares the actual value with the

Table 5.1 Study-characteristics and baseline characteristics of the enrolled adolescent (13 to 17 years old) participants in the studies ASRA and TROIA for inpatients and EvAKuJ for outpatients comparing non-morbid and morbidly obese patients

	ASRA	TROIA	EvAKuJ
Treatment setting	Inpatient	Inpatient	Outpatient
No. of centers	8	3	43
Enrollment	2002–2003	2007–2009	2006–2007
Age-range	13.0–17.0	13.0–17.9	13.0–16.9
Non-morbidly obese adolescents			
N	270	202	265
Female sex	60 %	64 %	57 %
Age mean(SD)	14.4 ± 1.0	15.1 ± 1.3	14.4 ± 1.0
BMI (kg/m^2)	32.5 ± 3.1	32.7 ± 3.6	30.2 ± 3.3
BMI-SDS t0 (AGA)	2.60 ± 0.35	2.96 ± 0.32	2.30 ± 0.44
Follow-up 1 year	81 %	54 %	42 %
Morbidly obese adolescents			
N	40	69	24
Age mean(SD)	14.8 ± 1.1	15.4 ± 1.4	15.0 ± 1,2
Female sex	63 %	58 %	88 %
BMI (kg/m^2)	43.4 ± 4.6	43.7 ± 4.3	42.1 ± 4.4
BMI-SDS t0 (AGA)	3.51 ± 0.31	3.55 ± 0.20	3.52 ± 0.23
Follow-up 1 year	75 %	54 %	33 %

tracking BMI by forming the percentage change of BMI as is the custom in adults. The consistency with the adult definition is especially important in adolescents with extreme obesity—a chronic disorder that is bound to persist into adulthood and that thus will require a transition from pediatric to adult care.

5.2.3 Patients

Baseline characteristics of the subjects in the three studies are presented in Table 5.1. For details, I refer to the original publications of the three studies (Hoffmeister et al. 2011; van Egmond-Fröhlich et al. 2006; 2013). All three studies required that patients be suited for group therapy and excluded for secondary and syndromal obesity. For the purpose of our analysis only data of patients aged 13.0 to 18.0 years were included.

5.2.4 Inpatient Treatment

The selected treatment centers in both the ASRA (van Egmond-Fröhlich et al. 2006) and TROIA (van Egmond-Fröhlich et al. 2013) studies all offered inpatient multimodal weight loss treatment for children and adolescents. Treatment

was not experimentally influenced by a study protocol. The three institutions in the TROIA study based their treatment on the same framework manual (Stachow and Flothkötter 2004) and adhered to the same guidelines (Mayer and Wabitsch 2007); therefore intensity and focus were similar. The training sessions for patients were performed in groups of 8–12 patients. Treatment consisted of sports therapy, physical activity counseling by sport therapists, dietary counseling, psychological interventions, and psycho-education regarding the medical consequences of obesity. In addition, physically active leisure time activities, supervision of meals, and an energy-reduced nutritionally optimized diet were provided. Parents received written materials and, in addition, face-to-face counseling on admission and at discharge. The eight contributing institutions in the ASRA study had similar but less homogeneous treatment concepts as this study partly preceded the development of guidelines for inpatient treatment in Germany.

5.2.5 *Outpatient Treatment*

We refer to the original publication of the EvAKuJ study (Hoffmeister et al. 2011) for a detailed description. In brief, the selected treatment centers were all offering multimodal outpatient weight loss treatment for children and adolescents under inclusion of their parents. Treatment was not experimentally influenced by a study protocol as the study was designed as an observational survey capturing the current status of obesity care in Germany. Therefore, intensity and focus varied between treatment centers.

5.2.6 *Measurements and Procedures*

Weight and height were measured at the treatment centers at baseline (t0), at the end of treatment (t1), and at the treatment center or with the primary physician at a 1-year follow-up (t2). BMI-SDS was calculated using the LMS method based on the KIGGS BMI reference (Kurth and Schaffrath Rosario 2007). Tracking BMI was calculated for the time of a 1-year follow-up measurement based on the BMI-SDS value at baseline. Age adjusted percent BMI change was calculated as

$$\Delta\text{BMI\%adj} = (\text{BMI(t2)} - \text{BMI(tracking)})/(\text{BMI(tracking)} * 100).$$

5.2.7 *Statistical Analysis*

Failure was defined as ΔBMI%adj ≥ 0, little success as ΔBMI%adj <0 % but ≥ -5 %, moderate success as ΔBMI%adj < -5 % but ≥ -10 %, and great success as ΔBMI%adj < -10 %.

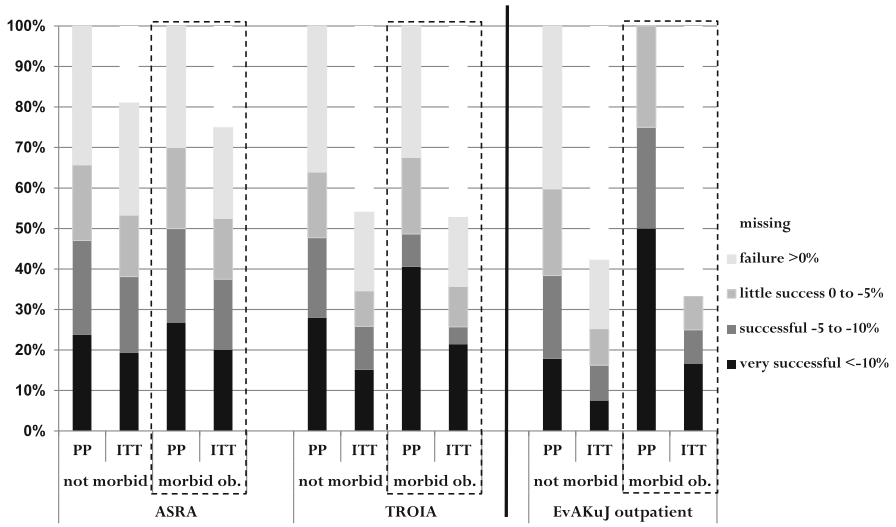

Fig. 5.3 This figure shows the success rates for all three studies and for both non-morbid patients and morbidly obese adolescents. Sucess rates are shown using the per protocoll (which optimistically ingnores missing values) and the intention-to-treat method where patients with missing follow-up data are pessimistically coded as treatment failures. The truth must lie somewhere in between. Morbidly obese profit at least as much from treatment as lesser degress of obesity. There is no clear difference between in- and outpatient treatment, but the outpatient treatment data suffer from lower numbers and poorer return rates

Success rates were both calculated as intention to treat (where missing follow-up data are pessimistically depicted as failures) and per protocol (where patients with missing values are optimistically assumed to have the same success rates as patients whose data were measured).

For per protocol analysis success rates were compared by ordinal logistic regression with success category as dependent variable, morbid vs. non-morbid obesity as independent variable, and age and sex as covariates for each study. For intention-to-treat analysis we defined success as $\Delta\text{BMI\%adj} < -5$ % and coded missing data as failure. With this dependent variable we performed logistic regression for each study, using morbid vs. non-morbid obesity as independent variable, and age and sex as covariates.

5.3 Results

Success rates did not differ significantly between morbidly and non-morbidly obese adolescents in either study and with either intention-to-treat or per protocol analysis (see Fig. 5.3). This results is qualitatively unchanged if morbid obesity is defined by a BMI > 40 kg/m^2 and success by a decline in BMI by 5 % without age adjustment.

For morbidly obese adolescents success rates defined as improvement of age-adjusted BMI by at least 5 % ranged from 37 % to 50 % in ASRA, from 24 % to 48 % in TROIA, and from 24 % to 74 % for EvAKuJ (i.e., between the pessimistic ITT and the optimistic PP analysis results). In this long-term successful subgroup of morbidly obese adolescents average improvement of age-adjusted BMI was 14 % for ASRA, 16 % for TROIA, and 20 % for EvAKuJ.

In both the inpatient study TROIA (van Egmond-Fröhlich et al. 2013) and the outpatient setting of EvAKuJ (van Egmond-Fröhlich et al. 2006), higher impulsivity/inattention, as measured by the parent rated hyperactivity subscale of the Strengths and Difficulties Questionnaire, was significantly associated with poorer long-term weight loss success. This effect is stronger in adolescents than in children. As there was no interaction with the severity of obesity, these results should be valid for morbidly obese adolescents.

5.4 Conclusions

We firstly propose a definition of morbid obesity based on (IOTF) back-extrapolation of grade III obesity (BMI 40 kg/m^2) based on the current national BMI population reference as this definition is continuous with the adult definition and takes the age dependence of BMI into account.

We secondly propose the definition of success for morbidly obese adolescents using age-adjusted ΔBMI% based on a current BMI population reference as this method avoids age and severity dependence in the calculation of long-term weight change. For older adolescents the adult cutoffs and unadjusted ΔBMI% may be used instead. The cutoffs for (age-adjusted) ΔBMI% should be harmonized with the adult definitions of (0 %), –5 %, and −10 %. As only long-term maintenance of weight change is effective in the prevention of metabolic and other biopsychosocial comorbidities of obesity, we propose using a follow-up measurement at least one year after the termination of treatment.

Using these proposed methods, we showed in both in- and outpatient settings that the success rates of conservative treatment in morbidly obese are at least as good as with lesser severity.

Even in the successful subgroup the reduction in overweight is smaller (15–20 %) than in surgical studies, but this should still adequately reduce comorbidity in most cases and it will also buy time. Time until the patient matures and is more able to handle his problem (as may be the case in later adolescence) or is better able to understand the consequences of surgery. It may also grant us the necessary time to improve our treatment methods and our knowledge about long-term effects and side effects of treatments.

As yet, there is no evidence base for the differential indication between in- and outpatient treatment [there are no RCT studies comparing settings and the EvAKuJ study did not detect any significant interaction between baseline predictors of

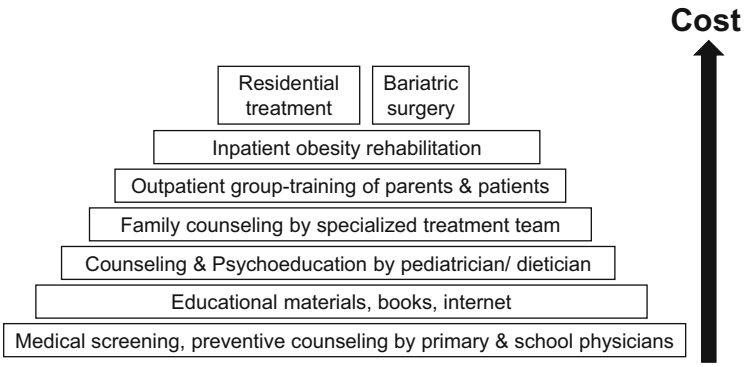

Fig. 5.4 Management Pyramid. Management options with higher cost are at the *top*. Higher level treatment options should be reserved to cases with higher severety and comorbidity usually after lower level options are exhausted

treatment success and treatment setting regarding weight-related success (Wabitsch and Moss 2009; van Egmond-Fröhlich et al. 2006)].

Currently inpatients are on average more severely obese, older, and of lower socioeconomic status (Reinehr et al. 2009; van Egmond-Fröhlich et al. 2007). Thus, most morbidly obese adolescents entering interdisciplinary group treatment in Germany do so in an in- rather than outpatient setting. While there is no clear consensus on differential criteria for outpatient, inpatient, and bariatric treatment options some general statements may be put forward:

- Inpatient rehabilitation may be most appropriate for morbidly obese adolescents where available outpatient options were exhausted and ineffective, medical comorbidites require rapid weight loss, or parental support is inadequate for intensive outpatient treatment. It should be followed up by long-term outpatient maintenance therapy. There are ongoing efforts to further improve the cooperation between inpatient and outpatient treatment facilities.
- Our results support the current AGA statement on bariatric surgery that requires that conservative treatment options have to first be exhausted, which in Germany includes inpatient treatment options, before surgery is considered. Further research may show that certain morbidly obese adolescents (e.g., with mental handicap or syndromal etiology) may require bariatric surgery in most cases.

This stepwise approach is best illustrated by the treatment pyramid (Fig. 5.4).

Long-term (>5 years) follow-up data on a statistically meaningful group of morbidly obese adolescents treated conservatively and surgically are lacking. The AGA therefore supports the ESPED registry of all such patients in Germany.

For this purpose, the methods for comprehensive evaluation that goes beyond the weight-related success and, e.g., includes tests of physical fitness, weight-related behavior, quality of life, and psychosocial health need to be standardized. The innovative comprehensive obesity evaluation system AdEVA from Austria that can be used in children and adolescents as well as in adults should be integrated (Ardelt-Gattinger and Meindl 2009).

We have contributed to the mounting evidence on the detrimental influence of impulsivity/inattention or attention-deficit/hyperactivity disorder (AD/HD) on conservative treatment in both the pediatric age range (Hoffmeister et al. 2011; van Egmond-Fröhlich et al. 2006; Nederkoorn et al. 2006a, b) and in adults (de Zwaan et al. 2011; Pagoto et al. 2010). Obesity in adolescents (Waring and Lapane 2008; Lam and Yang 2007; Erhart et al. 2012) and adults (de Zwaan et al. 2011; Pagoto et al. 2009) appears to be associated with AD/HD. AD/HD prevalence may be even higher in morbidly obese patients (Agranat-Meged et al. 2005; Fleming et al. 2005), affecting up to 30 % of individuals. Therefore screening for AD/HD and impulsivity/inattention should be mandatory. We need to research how to address this problem in the obesity treatment programs (including possible medical treatment).

Preventive societal environmental changes would not only help prevent morbid obesity but also facilitate weight loss especially in adolescents with poor self-control.

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Chapter 6
Comorbidities: Non Alcoholic Fatty Liver in Childhood Obesity

Birgit Jödicke and Susanna Wiegand

6.1 Introduction

Obesity poses increasing challenges to most healthcare systems worldwide (Wang and Lobstein 2006). The growing epidemic of overweight and obesity in childhood and adolescence has raised global concern among experts, as the numbers of affected children and adolescents steadily increased over time. The increase in prevalence of childhood obesity due to obesogenic environmental conditions (i.e., increased consumption of processed food including fructose containing juices and sweets, physical inactivity) results in a rising prevalence of metabolic syndrome (Weiss et al. 2004; Baranowski et al. 2006) and type 2 diabetes in populations other than minority groups (Wiegand et al. 2004; I'Allemand et al. 2008). The major diagnostic and therapeutic challenges posed by obesity comorbidities have been a constant focus of the pediatric discourse, since obese children and adolescents present numerous comorbidities. Commonly psychosocial (*poor self-esteem*, *depression*, *eating disorders*), neurological (*pseudotumour cerebri*), pulmonary (*sleep apnoea*, *exercise intolerance*),cardiovascular (*dyslipidemia*, *hypertension*), endocrine (*type 2 diabetes*, *precocious puberty*, *polycystic ovary syndrome in girls, and hypogonadism in boys*), musculoskeletal (*slipped capital femoral epiphysis*, *flat feet*), renal (*glomerulonephritis*), and gastrointestinal (*gallstones*) comorbidities are among those most frequently observed (Ebbeling et al. 2002). The majority of the

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examples above belong to the subgroup of metabolic comorbidities with the metabolic syndrome as a risk cluster for the development of cardiovascular diseases. This chapter will put an emphasis on the hepatic manifestation of the metabolic syndrome, namely, the *Nonalcoholic Fatty Liver Disease*.

Nonalcoholic fatty liver disease (NAFLD) is one of the consequences of the current obesity epidemic and the hepatic manifestation of the metabolic syndrome. Simple steatosis can progress to nonalcoholic steatohepatitis (NASH) characterized by steatosis, inflammation, and progressive fibrosis, ultimately leading to cirrhosis and end-stage liver disease. NASH was first observed in children in 1983 as a pattern of liver injury (Moran et al. 1983). NASH can even develop in obese children under 10 years of age (Patton et al. 2006). An enlarged, echogenic liver shown by ultrasonography in obese children and adolescents is highly suggestive of NAFLD or NASH. Histological confirmation of NASH is still the gold standard used to accurately assess the degree of steatosis, inflammatory lesions, and fibrosis found in NASH and to distinguish NASH from simple steatosis. Liver stiffness measurement using fibroscan may be a promising new sonographic alternative tool for diagnostic purposes in the near future (De Lèdinghen et al. 2007).

In a recent study, 176 obese children and adolescents with elevated aminotransferases underwent liver biopsy and the clinical correlates of pediatric NASH were analyzed. Levels of aspartate-aminotransferase (AST), alanine-aminotransferase (ALT), and gamma-glutamyltransferase (GGT) were recorded because of their correlation with fibrosis severity. However, the sensitivity and specificity of this diagnostic test were not sufficient enough to replace liver biopsy in evaluating pediatric NASH in all patients (Patton et al. 2008).

6.2 Epidemiology

There are a few population-based studies in this field, such as data from the USA (NHANES III) (Fraser et al. 2007), where the prevalence of elevated ALT levels (>30 U/L) was 7.4 % among white adolescents, 11.5 % among Mexican-American adolescents, and 6.0 % among black adolescents. Elevated ALT levels were present in 12.4 % of male subjects compared to 3.5 % of female subjects. Most prevalence studies have been conducted in cohorts of children selected for overweight or obesity. By using elevated ALT as a surrogate marker of NAFLD, the prevalence varies between 10 % and 25 % (van Vliet et al. 2009) in different studies. A recent critical review of ALT screening for chronic liver diseases in adults confirmed that this type of screening has high specificity and good sensitivity and is a cost-effective method to detect liver diseases including consequences of metabolic syndrome and diabetes mellitus type 2 (Wedemeyer et al. 2010).

In a retrospective review of 742 children (aged 2–19 years) who had an autopsy (after death or suicide), Schwimmer et al. (2006) found that the prevalence of NAFLD increased with age (0.7 % for ages 2–4 years and 17.3 % for ages 15–19 years). They were also able to show a significant difference in prevalence by race

and ethnicity (black: 1.5 %; white: 8.6 %; Asian: 10.2 %; Hispanic: 11.8 %). They found the highest prevalence of NAFLD in children and adolescents who were obese (38 %), decreasing in those being overweight (16 %) or normal weight (5 %). Surprising was the result that fatty liver is the most common liver abnormality in children aged 2–19 years. The presence of macrovesicular hepatic steatosis in approximately 1 of every 10 children has important consequences for the long-term health of children and young adults. Gender-specific fatty liver prevalence rates were found by Denzer et al. (2009) in 532 obese children and adolescents (291 girls) as follows: NAFLD was significantly higher in boys (41.1 % compared to girls 17.2 %) and was highest in post-pubertal boys (51.3 %) and lowest in post-pubertal girls (12.2 %). The severity of the steatosis was shown to be associated with increased visceral fat mass, insulin resistance, lower adiponectin levels, and higher blood pressure. Additional associated factors in boys were inflammation and steroid hormones.

Concerning the estimated prevalence of NAFLD in obese children and adolescents in Europe, an analysis was conducted based on APV-cohort data from more than 50,000 pediatric patients from Austria, Switzerland, and Germany and data from the KIGGs Cohort—a population-based survey for children and adolescents in Germany (Wiegand et al. 2011). Gamma-glutamyl transferase (GGT) and the aminotransferases were used as surrogate markers and 50 U/l defined as the cutoff level (corresponding to at least a 1.5-fold elevation). GGT is an independent predictor of long-term outcome in adults. Data in pediatric cohorts in this respect are rare. We studied 24,000 children and adolescents (13,000 KIGGs/11,000 APV). GGT was elevated in 1.3 % (0.3 % KiGGS/2.5 % APV) and was strongly associated with the degree of obesity and male gender (Fig. 6.1).

Because in KIGGs only GGT was measured, the aminotransferases could only be analyzed in the APV cohort. Results show that NAFLD was present in 11 % of the study population, but predominantly in boys (boys vs. girls: 14.4 % vs. 4 %; $p < 0.001$) in extremely obese (Xob) (obese vs. Xob: 9.5 % vs.17.0 %; $p < 0.001$) and in older age (<12 vs. >12 years of age 8.0 % vs. 12.0 %; $p < 0.001$; adjusted for BMI). ALT >50 U/l was significantly associated with fasting insulin and BMI-SDS. In multiple logistic regression models again Xob and male gender were strongly associated with NAFLD (odds ratio Xob vs. normal weight = 3.2; odds ratio boys vs. girls = 2.3). The results underline the epidemiological dimension of this obesity-related morbidity even in childhood. Therefore, at least ALT is recommended as a screening parameter in basic care of children and adolescents. If data using the aminotransferases as a surrogate marker are compared to histological data, it seems that the prevalence of NAFLD in childhood and adolescents is probably largely underestimated.

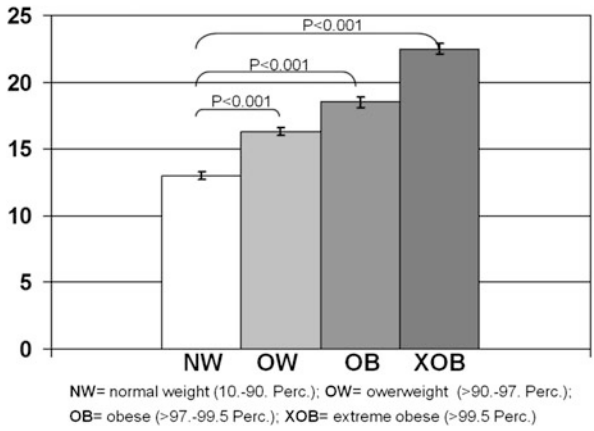

Fig. 6.1 GGT according to weight categories, adjusted for age and gender (reference 10-year-old boy): Least square means [adapted from Wiegand et al. (2011)]

6.3 Diagnosis

There is a distinction between two *Nonalcoholic Fatty Liver Diseases* (NAFLD):

- The Nonalcoholic Fatty Liver is defined as the excessive deposit of fat in the liver (>5 % of the hepatocytes containing macrovesicular fat) leading to macrovesicular hepatic steatosis in the absence of significant alcohol consumption. This is an "umbrella" term which includes a range of disease severity from the simple form of steatosis to nonalcoholic steatohepatitis.
- The *Nonalcoholic Steatohepatitis* (NASH) in addition calls for signs of inflammation and scarring, i.e., fibrosis. This more severe disease form can lead to progressive liver injury resulting in cirrhosis and hepatocellular carcinoma.

Alcoholic hepatitis (as seen in adults) is almost nonexistent in children; however, in the adolescent population the abuse of alcohol is a rising concern and should therefore be at least considered. Significant alcohol consumption may be defined as more than 20 g of alcohol/day in women and >30 g/day in men (Seth et al. 2011a). Additionally, any alternative causes of chronic liver disease such as hepatitis B and C, autoimmune hepatitis, alpha-1 antitrypsin deficiency, cystic fibrosis, Wilson disease, and drug toxicity need to be excluded (Devadason and Scheimann 2012).

The *clinical presentation* of the Nonalcoholic Fatty Liver Disease is usually asymptomatic. However, abdominal pain in the upper right quadrant along with neuropsychological signs as irritability, fatigue, sadness, disorders of concentration, and sleep may actually be present in as many as 30 % of affected children and adolescents (Kistler et al. 2010).

Leading clinical signs may be hepatomegalia (enlargement due to fatty infiltration of the liver parenchyma) and acanthosis nigricans (cervical, inguinal, and/or axillary discoloration of unknown pathophysiological origin as a sign of insulin resistance) (Fig. 6.2).

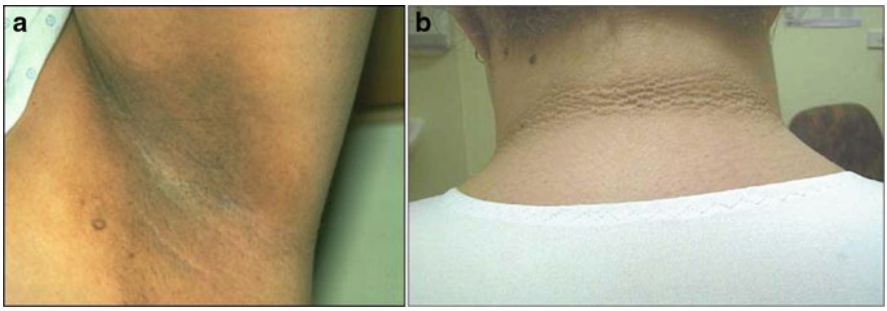

Fig. 6.2 Axillary (**a**) and cervical (**b**) acanthosis nigricans

Routine diagnostic procedures definitely include the serum aminotransferases ALT and AST. Clinical suspicion of NAFLD should arise as soon as these parameters exceed values of 50 U/l. They are however unspecific parameters of liver injury and are only considered to be surrogate markers. Results of a study on 16,390 patients (Wiegand et al. 2010) showed a NAFLD prevalence of 11.0 %, significantly more frequent in extremely (X) obese adolescents (obese vs. Xobese 9.5 %: 17.0 %, $p < 0.001$) and in older age (<12 vs. >12 years 8 %: 12 %; $p < 0.001$) and twice as high in boys as in girls (14.4 vs. 7.4 %, respectively; $p < 0.001$). With regard to this gender difference in the prevalence of ALT elevation, gender-related cutoffs of ALT have been suggested (>30 U/l for boys and >19 U/l for girls) (Di Bonito et al. 2010). A lower percentage of patients younger than 12 years of age, however, seem to exhibit significantly lower elevations of aminotransferases as compared to children aged 12–16 or 17–20 years (8.8 % vs. 12.2 % and 20.0 %, respectively; $p < 0.001$) (I'Allemand et al. 2008) (Fig. 6.3).

Diagnostic criteria also include the occurrence of any *components of the metabolic syndrome*, because NAFLD is the "hepatic manifestation" of the metabolic syndrome. As such, any of the five components of the metabolic syndrome (hypertension, BMI >97th percentile, elevated triglycerides, decreased HDL cholesterol, hyperuricemia)—especially when found in combination—may be a lead in detecting NAFLD (Kelishadi et al. 2009).

The typical "bright liver" appearance in an *abdominal ultrasound* is present if more than 30 % of the liver is affected by steatosis. In obese children and adolescents the enlargement and echogenic appearance of the liver as shown by ultrasonography are highly suggestive for manifest NAFLD and NASH. Scoring of liver steatosis determined by ultrasound is graded from zero to three, describing the echogenicity of the tissue. In addition, the venous blood flow should be measured (Shannon et al. 2011; Schwimmer et al. 2008) (Table 6.1).

However, this noninvasive procedure is not capable of differentiating between steatosis and fibrosis.

Hence, a definitive diagnosis can only be reached by histological confirmation (*biopsy*). To accurately assess the degree of steatosis, inflammation lesions, and

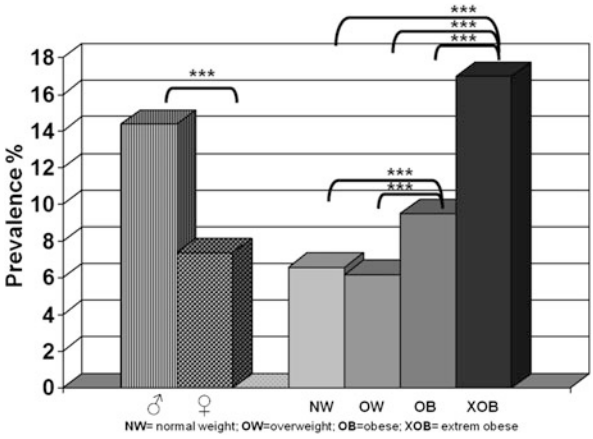

Fig. 6.3 Prevalence of NAFLD in relation to gender and weight categories (***$p < 0.001$ significant difference in the Kruskal–Wallis test [adapted from Wiegand et al. (2010)]

Table 6.1 Scoring of liver steatosis determined by ultrasound

Scores	Echogenicity of liver parenchyma	Visualization of diaphragm and intrahepatic vessels
Score 0 (normal)	Normal	Normal
Score 1 (mild)	Slightly increased	Normal
Score 2 (moderate)	Markedly increased	Slightly decreased
Score 3 (severe)	Severely increased	No or severely decreased

Adapted from Shannon et al. (2011)

staging of fibrosis, the gold standard to date remains the histological confirmation performed on biopsy material from the liver. This is *the* essential procedure so far in differentiating NASH from simple steatosis of the liver (Schwimmer et al. 2005; Schwimmer 2007).

Additional diagnostic parameters seem to be the waist-to-hip ratio, the HOMA-IR, and adiponectin levels. Also the gamma-glutamyl transferase >50 U/l is strongly associated with the degree of overweight (extreme obesity (OR 27.1) and male sex (OR 2.60). However, the prevalence of NAFLD could be largely underestimated by using surrogate markers for detection (Maffeis et al. 2011).

In a large European pediatric obesity cohort from the APV-Database, using elevated AST/ALT as screening parameters, the prevalence was significantly lower than in Schwimmer et al.'s autopsy study (11 vs. 37 %) and related to extreme obesity, male gender, and older age (Wiegand et al. 2010).

Because these screening parameters are not able to determine the degree of fibrosis and hepatocyte apoptosis, *noninvasive biomarkers* are one important topic for research in this field:

The *enhanced liver fibrosis test* (ELF) is a score including three serum markers combined in an algorithm to predict liver fibrosis.

The ELF was validated in 112 pediatric patients with biopsy-proven NAFLD and showed to be highly predictive of fibrosis (Nobili et al. 2009).

The Enhanced Liver Fibrosis Test (ELF) includes:

- Hyaluronic acid
- Amino-terminal propeptide of collagen type III (PIIINP)
- Tissue inhibitor of metalloproteinase (TIMP-1)

However, the study of Nobili et al. included only few patients with moderate or severe fibrosis.

The *serum Cytokeratin-18* (CK18) is a protein filament cleaved by captase-3 during apoptosis and then released into the circulation. In a multicenter validation study serum levels of CK18 were found to predict the presence of NASH and to determine its severity. Feldstein et al. (2009) published data comparing CK18 levels in 139 patients with biopsy-proven NAFLD versus 150 healthy controls. Serum levels of CK18 were found to predict both the presence of NASH and its severity. However, since CK18 is a marker for apoptosis which is seen in many types of liver disease, CK18 will most likely serve only as a measure for disease severity once the diagnosis of NAFLD has already been confirmed.

The ultrasound-based acoustic radiation force impulse *elastography* is a new type of imaging technique, presenting quite promising preliminary results concerning the noninvasive staging of liver fibrosis (Yoneda et al. 2010).

6.4 Pathology

The simple steatosis of NAFLD can progress to Nonalcoholic Steatohepatitis which is characterized by steatosis along with inflammation and progressive fibrosis, ultimately leading to cirrhosis and end-stage liver disease (Carter-Kent et al. 2008). As many as approximately 25 % of NASH patients might eventually progress to cirrhosis and consequently be confronted with complications like portal hypertension, liver failure, and hepatocellular carcinoma (McCullough 2006).

In literature on NASH the "two-hit" theory has been well described and has subsequently been replaced by a multiple-hit hypothesis. This postulates the progression from simple steatosis to NASH, fibrosis, and eventually cirrhosis. The "first hit" is defined as an accumulation of excessive fat in liver parenchyma—due to insulin resistance. This first step towards NASH is often already present in patients with a metabolic syndrome and, although it might not be enough to cause actual NASH, it may be sufficient to predispose for chronic hepatic inflammation. Several groups have indicated that the progression from NAFLD to NASH necessitates multifactorial complex interactions between genetic determinants, nutritional factors, and dysmetabolism (Malaguarnera et al. 2009). The genetic compound, however, seems to be quite substantial. Why some patients progress to cirrhosis and others do not, however, remains to a great extent unclear (Daly et al. 2011a). The "second hit" is assumed to be due to the oxidative stress generated

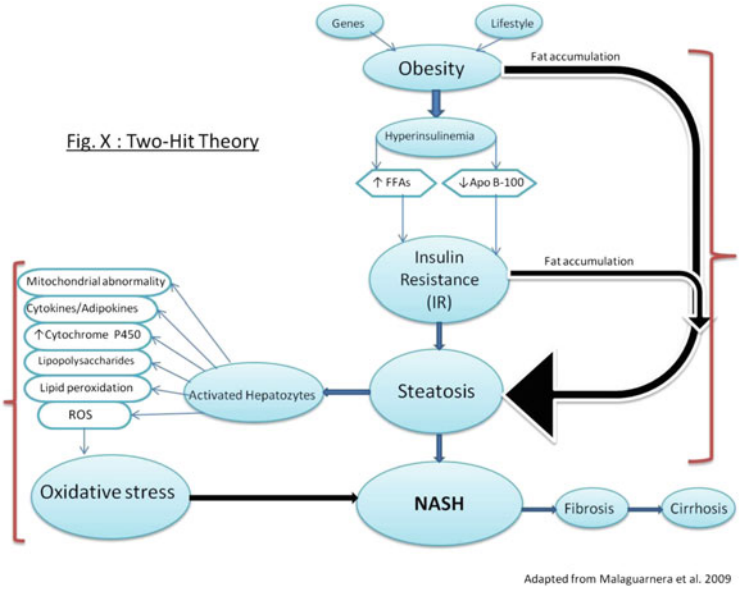

Fig. 6.4 Two-hit theory

by the reactive oxygen species (ROS) (Koek et al. 2011) of gut-derived lipopolysaccharides and soluble mediators which are synthesized from cells of the immune system as well as from cells of the adipose tissue (Ibrahim et al. 2011) (Fig. 6.4).

Pathophysiologically, the primary mechanism for progression from NAFLD to NASH is the functional impairment of liver cell organelles involving the production of ROS. The resulting activation of hepatocellular defense programs accumulating in the deterioration of organelle function (mitochondria) and the activation of kupfer cells produce inflammatory mediators. In turn, these mediators activate hepatic stellate cells to synthesize collagen, the overproduction of which leads to fibrosis and cirrhosis (Seth et al. 2011b).

Once Nonalcoholic Steatohepatitis has been diagnosed, the histopathological classification into two types of NASH is of importance. Type 1 is characterized by ballooned hepatocytes and/or perisinusoidal fibrosis along with simple steatosis (in the absence of portal features), while type 2 shows steatosis along with periportal inflammation and/or periportal fibrosis (in the absence of ballooning degeneration and perisinusoidal fibrosis). In a study analyzing 100 biopsies of children with NAFLD, Schwimmer et al. showed in 2005 that type 1 NASH was present in 17 % and type 2 in 51 % of children; 16 % showed overlapping features of both type 1 and type 2 and the remaining 16 % only presented signs of simple steatosis. Hence, type 2 is the predominant type of NASH seen in children (Fig. 6.5).

Many patients with hepatic steatosis do not develop NASH, suggesting that environmental and/or genetic factors modulate progression of the disease (Tilg and

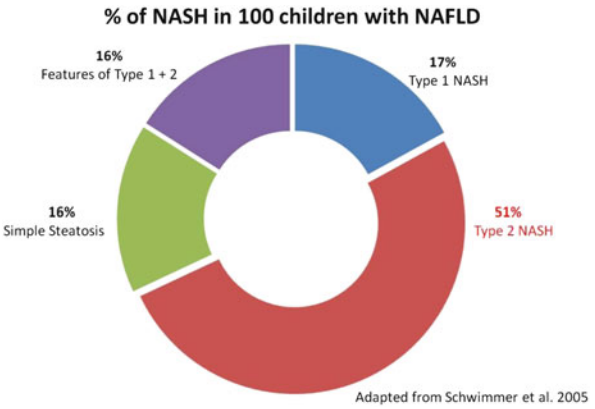

Fig. 6.5 Distribution of different forms of steatohepatitis

Moschen 2010). Although environmental factors and behavior seem to play a major role in NAFLD the most substantial part of the cause seems to be a *genetic disposition*. Environmental and behavioral factors may be considered, as well as bacterial overgrowth of the small intestine, obstructive sleep apnea syndrome, diet, and exercise. Family studies and interethnic variations in susceptibility to NAFLD or even NASH suggest that the genetic factor may determine the disease risk (Daly et al. 2011b). Some preliminary data suggest a linkage of patatin-like phospholipase 3 (PNPLA3) and the increased hepatic fat content and degree of hepatic inflammation as indicated by serum ALT levels. The allele was shown to occur most commonly in the group of Hispanic patients, who also seem to be the most susceptible ethnic group for NAFLD (Goran et al. 2010).

Some apolipoprotein C3 gene variants seem to be associated with NAFLD and insulin resistance, as carriers of the variant alleles C-382T, T-455C, or both showed an increase in fasting triglyceride levels of 60 % and NAFLD prevalence of 38 % compared to 0 % among wild-type homozygote controls (Kozlitina et al. 2011).

6.5 Therapy

In general, public health awareness and intervention are needed to promote healthy diet, exercise, and lifestyle modifications to prevent and reduce the burden of disease in the community. Furthermore, increasing evidence in obese adolescents demonstrates the benefits of lifestyle change as a treatment strategy for obesity-related comorbidities. NAFLD is largely reversible after successful lifestyle intervention. Several studies have shown that aerobic types of exercise are protective against age-related increases in visceral adiposity in growing children and adolescents. If NAFLD is already present, a controlled aerobic exercise program, even without weight loss, reduced hepatic and visceral fat accumulation and decreased insulin resistance in obese adolescents (van der Heijden et al. 2010). Addressing

both diet and physical activity, a 1-year nutrition-behavior intervention based on normocaloric balanced diet and physical exercise significantly reduced liver fat in obese children (Pozzato et al. 2010). Lifestyle intervention with diet and increased physical activity aiming at inducing weight loss is associated with significant improvements in liver histology and laboratory abnormalities in pediatric NAFLD. Additional antioxidant therapy with alpha-tocopherol plus ascorbic acid does not seem to increase the efficacy of lifestyle intervention alone (Nobili et al. 2008).

In unsuccessful cases of lifestyle intervention various pharmacological options for the treatment of NAFLD were tested, mainly in adults.

To study whether obese children and adolescents with NAFLD would benefit from pharmacological intervention, a randomized, double-blind, placebo-controlled clinical trial with vitamin E or metformin was conducted in 173 patients (aged 8–17 years) with biopsy-confirmed NAFLD. As a result, sustained reduction of ALT level was similar to placebo in both the vitamin E and metformin treatment groups. Neither vitamin E nor metformin was superior to placebo in attaining the primary outcome parameter (decrease of ALT level) (Lavine et al. 2011).

A random effects meta-analysis was performed to study the efficacy of insulin-sensitizing agents on histological and biochemical outcome in randomized control trials of biopsy-proven NASH in adults. The results showed that treatment with glitazones, but not metformin, demonstrates a significant histological and biochemical benefit, especially in patients without diabetes (Rakoski et al. 2010). Finally, the effect of probiotics was proven. In this sense, lactobacillus rhamnosus (strain GG) warrants consideration as a therapeutic tool to treat hypertransaminasemia in hepatopathic obese children who are noncompliant to lifestyle interventions. A study by Vajro et al. (2011) including 20 patients treated with lactobacillus rhamnosus strain GG or placebo for 8 weeks showed a significant decrease of ALT irrespective of changes of BMI z-score or visceral fat.

6.6 Summary and Outlook

Nonalcoholic Fatty Liver Disease (NAFLD) is the most common cause of pediatric liver disease closely related to childhood obesity. Especially post-pubertal obese boys are at risk for the development of NAFLD. The diagnostic panel should include all components of the metabolic syndrome.

Successful lifestyle intervention is most effective also for the therapy of NAFLD in obese children and adolescents.

Because of the impact on lifelong morbidity, there is urgent need for

- Noninvasive screening methods
- A better understanding of the metabolic situation in obese children
- Long-term follow-up of large pediatric cohorts
- Pediatric RCTs for therapeutic options
- Preventive strategies for high-risk groups.

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Chapter 7
Measurement of Atherosclerosis in Morbidly Obese Adolescents

Andrea Willfort-Ehringer and Michael E. Gschwandtner

Despite remarkable therapeutic advances over the past 50 years, cardiovascular diseases (CVD) are still the major causes of mortality and morbidity in the Western world.

This is the result of the increasing prevalence of atherosclerosis in the aging population and, above all, the under-recognition and under-treatment of individuals at risk for atherosclerosis. The atherosclerotic process begins during childhood (Raekallio et al. 1990; Pesonen et al. 1990; Stary 1989) and progresses silently over decades, long before it becomes symptomatic in the middle age of life. The first clinical manifestation of CVD might be severe and life threatening and may present as myocardial infarction or ischemic stroke in a rather advanced stage of disease.

Autopsy studies in children and adolescents, who died from accidental cause, showed antecedents of adult clinical symptomatic CVD in the aorta and in the coronary arteries in this early phase of life (Raekallio et al. 1990; Pesonen et al. 1990; Stary 1989). In these postmortem studies, the prevalence of atherosclerotic lesions was positively correlated with risk factors, such as obesity, lipid disorders, glucose intolerance, and smoking history (Pesonen et al. 1990).

During the past decades, morbid obesity (MO) became worldwide a primary child health problem. Four large longitudinal studies (Berenson et al. 1998; Davis et al. 2001; Magnussen et al. 2008; Raitakiri et al. 2003) demonstrated, by following thousands of schoolchildren up to their young adulthood, that obese children and adolescence are at high risk of becoming obese adults, and the more obese the child becomes, the greater the risk of obesity when they reach adulthood. MO is associated with an abnormal lipid profile, hypertension, insulin resistance, and hyperglycemia. This clustering of metabolic risk factors can be summarized as metabolic syndrome. The likelihood of development of CVD increases

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exponentially, in the presence of multiple risk factors, established for atherosclerosis. Taken together, severe comorbidities in morbidly obese patients are justifying the search for precursors of atherosclerosis in obese children and adolescents.

Traditionally, diagnosis of atherosclerosis was possible only at a rather advanced stage of disease, by angiographic measurement of atherosclerotic plaques, when patients got symptomatic. New technologies developed over the past decades made it possible even to detect very early stages of atherosclerosis (Groner et al. 2006; Urbina et al. 2009).

7.1 Assessment of Macrocirculation

The arterial wall is formed by three concentric layers: adventitia, media, and intima. The latter consists of a monolayer of endothelium cells, adjacent to the vessel lumen. The endothelium is like an endocrine organ, releasing substances such as nitric oxide (NO), prostacyclin, and endothelin to maintain the vascular tonus by vasodilatation or vasoconstriction, responding to physical and chemical signals. The underlying physiological phenomenon is the wall-shear-stress-induced endothelium-mediated vasodilatation, expressed by the ability of the endothelium to produce and to release NO, a potent vasodilator and an inhibitor of platelet aggregation, monocyte adhesion, and smooth muscle proliferation. Reduced ability of the endothelium to produce and/or to release nitric oxide is followed by the impaired ability of vasodilatation, so-called **endothelial dysfunction**, which is the earliest detectable alteration in macrocirculation on the pathway to manifest atherosclerosis. Celermajer was the first to describe a noninvasive method, the **endothelial-dependent flow-mediated vasodilation** (**FMD**), to evaluate the endothelial function, by high-resolution B-mode ultrasound of the brachial artery (Celermajer et al. 1992). The method consists in measurement of the increase in brachial arterial diameter with B-mode ultrasound, following 5 min of arterial occlusion at the forearm. Post-ischemic hyperemia induces increased wall shear stress and release of NO from the healthy endothelium, which causes smooth muscle dilatation and dilation of the arterial lumen. Interpreting FMD evaluation requires assessing endothelial-independent vasodilatation by application of an inorganic source of NO, glyceryl nitrate. Endothelial dysfunction can be clearly stated if only FMD is impaired, whereas nitrate-dependent vasodilation is considered as a measure for smooth muscle cell dysfunction (Corretti et al. 2002).

Several technical problems have limited the integration of the method into clinical routine. It is highly sonographer dependent and therefore requires extensive training. In addition there is a lack of methodical standardization and a variety of study protocols. FMD is influenced by multiple factors: the time of the day, the temperature in the laboratory, medication, antioxidants, caffeine, alimentary aspects (fat food or alcohol), hormone status, and exercise. All these factors have to be taken care of in the specific methodology (Corretti et al. 2002). Brachial FMD correlates with the endothelial function in the coronary circulation (Barton 2012)

and has shown to be a strong and independent predictor of cardiovascular events, inversely correlated to multiple traditional cardiovascular risk factors, such as morbid obesity and its comorbidities (Suwaidi et al. 2000).

The atherosclerotic process is triggered by chronic inflammation, whereas immune mechanisms interact with metabolic risk factors leading to cellular oxidation. Increased oxidative stress, similar in aging, leads to endothelial dysfunction, due to functional inactivation of NO by high concentrations of O_2. The similar mechanisms activated in obesity and in aging suggest that obesity in youth can be considered as accelerated "premature" aging, expressed by endothelial dysfunction and consequently by "premature" structural and morphological changes (Barton 2012).

Regardless of age, the mean FMD in healthy and non-obese children and adolescents is reported to be between 8 and 11 % with a wide range within the 95 % confidence interval between 4 and 18 %, however (Widlansky et al. 2003; Tounian et al. 2001; Kapiotis et al. 2006; Meyer et al. 2006a; Aggoun et al. 2008; Woo et al. 2004a). Studies on FMD in obese children and adolescents are rare and limited to a small number of included patients, however. FMD is demonstrated to be significantly lower in obese children and adolescents than in lean controls (Widlansky et al. 2003; Tounian et al. 2001; Kapiotis et al. 2006). Thus, reported by Kapiotis et al. in a study including a comparatively large number of obese children and adolescents: 154 obese subjects versus 54 lean controls with a mean FMD of 7.7 % (±6.14) vs. 11.1 % (±3.07) (Tounian et al. 2001). In some studies, both FMD and the nitrate-dependent dilation have been found to be lower in obese than in lean control children and adolescents (Tounian et al. 2001; Aggoun et al. 2008; Woo et al. 2004a; Kaufman et al. 2007; Ciccone et al. 2011; Zhu et al. 2005), so that one has to hypothesize that early functional changes of the arterial wall are not limited to the endothelium, however.

Lasting endothelial dysfunction under influence of cardiovascular risk factors leads to **mechanical changes**, due to changes of the elastic properties of the arterial wall, resulting in **stiffness or reduced distensibility**. Arterial walls stiffen with age caused by elastin fiber fatigue and fracture. These changes lead to increased pulse-wave velocity, especially along central elastic arteries, and increases in systolic blood pressure and pulse pressure. Elevated pulse pressure and systolic arterial hypertension play a major role in cardiovascular morbidity and mortality. Therefore, measures of arterial stiffness are strong predictors of future cardiovascular risk in adults (Laurent et al. 2001; Willum-Hansen et al. 2006).

Arterial stiffness can be assessed by using three groups of noninvasive methods (Urbina et al. 2009): analysis of the arterial pressure waveforms, calculation of the change in diameter of an artery (B-mode or M-mode ultrasound measurements of the change in lumen diameter from systole to diastole), and measurement of pulse-wave velocity (PWV), which turns out to be the most widely used method in adults (Asmar et al. 1995). The method is more independent on the operator and easily applicable, whereas the ultrasound methods are sonographer dependent and furthermore need special training.

PWV is a measure of the speed of the arterial pressure wave propagation and noninvasively recorded by using pressure-sensitive transducers. Measurements are usually made from the carotid to the femoral artery. The time delay from the proximal to the distal artery is measured and divided by the distance of the measurement sites to calculate the velocity. The higher the velocity, the stiffer is the arterial wall.

As reported by Wildman et al. (2003), excess body weight in adults, aged 20–30 years, is associated with higher aortic stiffness, which expresses the substantially high cardiovascular risk of this young cohort. Cardiovascular risk factors, such as obesity, identified in childhood and adolescence predict decreased carotid artery elasticity in adulthood (Willum-Hansen et al. 2006). These data suggest that risk factors operating in early life may have sustained destructive effects on arterial elasticity, which is inversely correlated to cardiovascular morbidity in adulthood. Regardless of the specific technique used for evaluation of arterial stiffness or decreased arterial distensibility, data on obese pediatric cohorts are limited. In a study on more than 500 healthy prepubescent children, carotid–femoral PWV was independently positively correlated with body mass index, waist circumference, and percentage body fat and inversely correlated to their cardiorespiratory fitness. The study shows a clear relationship among degree of body fat and arterial stiffness (Asmar et al. 1995). Arterial distensibility measured with ultrasound is impaired in the settings of pediatric studies with obesity (Tounian et al. 2001; Aggoun et al. 2008; Iannuzzi et al. 2004), elevated leptin levels (Singhal et al. 2002), increased blood pressure, and obesity-related hyperinsulinemia (Whincup et al. 2005; Urbina et al. 2010).

Prolonged endothelial dysfunction leads to structural alterations of the arterial wall, to **thickening of the intima-media layer**, which is the first morphological detectable change that can directly be measured by high-resolution B-mode ultrasound, as atherosclerotic plaque formation (Fig. 7.1).

The ultrasonic "double line" in the common carotid artery was first described in the early 1980s and has shown good correlation to histological findings (Pignoli et al. 1986). Rita Salonen was the first who associated carotid intima-media thickness (cIMT) with increased cardiovascular risk (Salonen and Salonen 1991). In the adult population measurement of cIMT is established as a marker of generalized atherosclerosis. As shown in a meta-analysis, including eight large clinical studies and more than 37,000 individuals, cIMT is as a strong and independent precursor of cardiovascular morbidity including ischemic stroke and myocardial infarction as well as cardiovascular mortality (Lorenz et al. 2007). Furthermore, cIMT has proven to be a reproducible and reliable parameter to detect changes over time (Kanters et al. 1997). Therefore it has been applied as an endpoint in clinical trials assessing the impact of pharmacological or lifestyle interventions in adults. Carotid IMT increases physiologically with age. In adults males have a more pronounced cIMT than age-matched females (Redberg et al. 2003). Similar to adult IMT, cIMT in healthy children is higher in boys than in girls and is increasing with age, as reported by Boehm et al. (Böhm

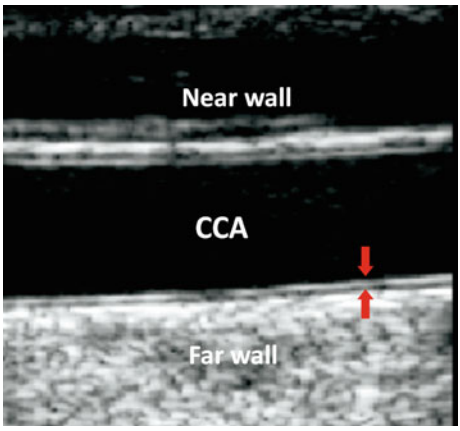

Fig. 7.1 (**a**) Duplex Ultrasound image in B-mode, longitudinal view: showing measurement of the carotid intima-media thickness at the far wall of the common carotid artery (CCA) by the "leading edge to leading edge" method, as pointed out by *red arrows*

et al. 2009). In a few studies including markedly smaller numbers of children and adolescents the latter is controversily discussed.

Different study protocols are used in adults and in pediatric cohorts, measuring the cIMT at different sites: at the common carotid artery (CCA) and at the internal carotid artery, at the carotid bulb, or at the CCA solely; it is measured at the far wall and at the near wall or at the far wall exclusively (Lorenz et al. 2007). A few authors measure at the common femoral artery or at the site of the abdominal aorta, but these sites seem to be not appropriate for evaluation of IMT for the morbidly obese youth, due to anatomical reasons.

Independent on the heterogeneity of the ultrasound measurement methods, cIMT is reported to be significantly increased in obese and overweight children and adolescents compared to lean and healthy controls in 22 of 26 studies, as reported by Lamotte et al. (2011). In two studies including normotensive obese children, no significant difference in cIMT was reported. Agoun et al. (2008) stated no significant difference in CIMT in a small group of prepubescent obese children, whereas half of them had systolic hypertension. Morrison et al. (2010) reported slightly but not significant increase in cIMT in the obese group compared to the healthy controls. Furthermore, there is evidence that in obese children with metabolic syndrome, cIMT is significantly more pronounced than in those without.

Taken together, impaired endothelial dysfunction and arterial distensibility as well as thickening of the intima-media layer of the arterial wall in overweight and obese children and adolescents are confirming early vascular damage and accelerated "premature" aging of the vasculature.

The research on **lifestyle interventions**, such as dietary modifications and/or exercise, in obese and overweight pediatric individuals during the past years gives evidence of potential improvement of impaired vascular health by lifestyle interventions.

Short-term lifestyle intervention by exercise training alone nearly normalizes brachial FMD after only 6–8 weeks of training, conducted 3 to 4 times a week (Kelly et al. 2004; Watts et al. 2004a, b). Reversal of the exercise-induced

improvement in endothelial function was observed after only 6 weeks of inactivity, leading to a recommendation for continuous exercise training.

Six weeks of a dietary intervention improved endothelial function in overweight and obese children aged 9–12 years (Woo et al. 2004b). From combinations of diet and exercise training similar short-term beneficial effects have been observed (Woo et al. 2004b; Pal et al. 2012), potentially exceeding those of dietary alterations or exercise training alone. Intervention by fiber supplementation over 6 weeks showed beneficial effect on blood pressure and short-term beneficial effect on arterial stiffness. In contrast, carotid IMT (Kelishadi et al. 2008) has not been shown to be responsive to short-term lifestyle interventions in this pediatric high-risk cohort. Longer-term interventions have demonstrated improvements both in cIMT and in FMD of overweight or obese youth (Kelishadi et al. 2008; Meyer et al. 2006b; Wunsch et al. 2006). Six months of exercise training improved FMD and carotid IMT in obese youth aged 11–16 years old, compared with age-matched controls (Kelishadi et al. 2008). Similar results have been documented in 9- to 12-year-old children following 12-month-long regimens of either dieting alone or diet and exercise, with the latter showing greater benefits than the former. However, a 12-month-long intervention in obese prepubescents that included exercise training and nutrition education showed improvements in brachial FMD and reduced cIMT only in those children who experienced substantial weight loss. This seems to be in contrast to a cohort of prepubertal obese children as reported recently. In these children with manifest arterial hypertension, no improvement of the impaired endothelial function but a significant reduction of the systemic blood pressure, the body mass index, the abdominal fat, and the arterial stiffness could be demonstrated, however (Farpour-Lambert et al. 2009).

Long-term lifestyle modifications (Lamotte et al. 2011) seem to keep the promise in reversing the impaired arterial health and atherosclerotic process of children and adolescent with obesity. We can only speculate on the underlying physiological mechanisms responsible for the favorable outcomes of lifestyle interventions in young obese.

Nevertheless, potential reversibility of arterial impairment in macrocirculation justifies the application of diagnostic tools in primary prevention in this high-risk group. On this basis the need for standardized diagnostic methods and reference values as well as an extensive operator training becomes obvious (Fig. 7.2).

7.1.1 Microcirculation

Microcirculation of human skin consists of two different networks—the superficial nutritive and the deeper subpapillary one. The later network consists of arterioles, venules, and arteriovenous shunts. A good portion of blood volume flows through this subpapillary network. In this network vessel walls are rich in smooth muscle cells. These muscle cells are responsible for regulation of blood flow. Therefore, if regulation of blood flow has to be investigated, one has to measure subpapillary

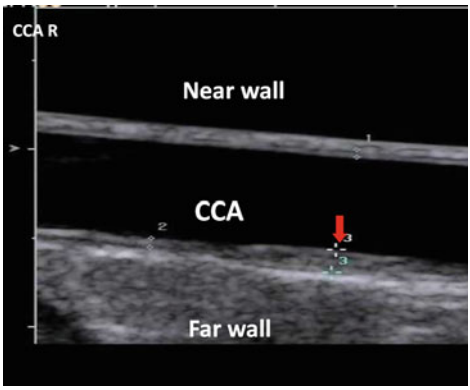

Fig. 7.2 A rare ultrasound finding in pediatric cohorts: advanced stage of atherosclerosis, an atheroma (*red arrow*) at the far wall of a right CCA in a 16-year-old boy with metabolic syndrome (BMI 39.5, hyperlipidemia, hypertension, and insulin resistance) in a longitudinal view

blood flow. Subpapillary blood flow can be examined by laser Doppler fluxmetry with a penetration depth sufficient to reach this deeper, subpapillary region. A laser Doppler is a noninvasive medical device that is able to assess total skin perfusion. After transmission of skin a laser beam (wavelength: 632 nm, power: 1 mW) becomes Doppler shifted by inference with moving blood cells. The Doppler shifted and reflected signal is picked up by a photodetector. There the beam is processed and mixed to form a photocurrent. The photocurrent scales linearly with tissue perfusion, which is defined as the product of average speed and concentration of blood cells.

In order to investigate microvascular (dys)function laser Doppler fluxmetry has to be combined with provocation maneuvers like iontophoresis or post-occlusive reactive hyperemia (PORH) (Morales et al. 2005). For that purpose PORH reflects the ability of microvascular vasoconstriction. Previous investigations showed an alteration of peak perfusion and recovery time in patients with advanced atherosclerosis compared to healthy controls (Morales et al. 2005). Furthermore, in the presence of diabetes, even ahead of clinically manifested atherosclerosis, microvascular dysfunction reflected by reduced vasoconstrictive ability during PORH was observed (Humeau et al. 2000).

Forty-one consecutive children, with morbid obesity (MO), a body mass index >99.5th percentile for age and gender, were examined at our laboratory (Yamamoto-Suganuma and Aso 2009). Ninety-one pupils of an Austrian secondary grammar school served as healthy controls with a BMI between the 10th and 90th percentile (2004). In our study we found relevant differences between children with MO and healthy controls: Peak perfusion was significantly higher in children with MO (1.67 ± 0.76 AU) as compared to healthy controls (1.26 ± 0.5 AU, $p < 0.001$). Consecutively, recovery time, time until average baseline perfusion has been reached after hyperemia, was longer in children with MO (118.21 ± 34.64 s) than in healthy controls (83.18 ± 35.08 s, $p < 0.001$). The significant difference of peak perfusion between the two groups remained after adjusting for LDL cholesterol and body height.

The higher peak perfusion during hyperemia and the prolonged recovery time in children suffering from MO can be interpreted as signs of an impaired vasoconstriction following ischemia. As possible explanation PORH might be divided into three phases emphasizing vasoconstriction as decisive mechanism: in the initial phase ischemia, induced by suprasystolic occlusion, provokes vasodilation as a result of acidosis and low oxygen and high carbon dioxide concentrations. In the second phase, immediately after cuff release peak perfusion is observed. Due to blood rheology, the Fahraeus–Lindqvist effect and the large cumulative diameter of capillaries precapillary vasoconstriction might rather lead to a decrease instead of an increase of blood flow velocity (Morales et al. 2005). Therefore, precapillary vasoconstriction, which is induced by endothelium-dependent myogenic response, seems to attenuate the initial increase of perfusion to counterbalance capillary hyperperfusion. Finally, during the third phase (recovery time) microcirculation regenerates again to its homeostasis. This third phase might be triggered by various mediators like nitric oxide, prostanoids, and adenosine and correlates with the level of peak perfusion (Schlager et al. 2011). Both a thickened arterial wall structure and endothelial dysfunction have been made responsible for this decline in microvascular functionality. Furthermore, microvascular dysfunction as described in obese adults was attributed to various mechanisms. Such mechanisms are the well-known risk factors of atherosclerosis like insulin resistance, hypertension, or dyslipidemia. Moreover, the production of adipokines and pro-inflammatory cytokines induces oxidative stress that finally leads to endothelial dysfunction (Binggeli et al. 2003).

Microvascular function seems to be impaired in children with MO when compared to healthy ones, which might be attributed to an impaired vasoconstrictive ability in microcirculation. This might be interpreted as an early sign of an emerging endothelial dysfunction.

Taken together, Laser Doppler fluxmetry appears as a promising and as an easily applicable technique to assess microcirculation in children and adolescents. Therefore, further studies should be performed to investigate early microvascular damage by specific metabolic disorders, to further elucidate the physiological pathway during PORH, and to evaluate potential reversibility by lifestyle interventions.

These noninvasive measurement tools, as discussed for evaluation of macro- and microcirculation, offer a new diagnostic approach for pediatricians with regard to the pandemic of childhood obesity, followed by therapeutic interventions to reduce or at least to stabilize vascular impairment.

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Chapter 8
Arthritis and Joint Problems in Morbidly Obese Adolescents

Harald K. Widhalm

8.1 Osteoarthritis

The term arthritis was originally used to describe degenerative diseases of peripheral joints mainly associated with hinge wear, inflammation and advanced age. Clinical practice, however, has shown that an increasing number of adolescents and young adults are already suffering from similar disease patterns. Consequently, terminology was adapted and the concept of osteoarthritis (OA) received entry into medical usage.

The aetiology of OA is characterized by mechanical abnormalities which result in permanently or at least periodically increased loading forces towards the joints. As a consequence of the mechanical stress an alteration of articular cartilage and subchondral bone occurs. This remodelling finally leads to a progressive degradation of the cartilage matrix with associated functional impairment of the affected joint. Additional damage by the exposure of subchondral bone accelerates the process of degeneration (Table 8.1).

Symptoms of joint deterioration usually develop gradually and worsen over time. The primary manifestation often involves pain, tenderness and swelling of the affected joints. In mild to moderate stages of OA the pain typically increases under strain and improves with rest. With progression of the disease, symptoms become more persistent and may lead to severe deformations. The consequences are limited ranges of motion, joint effusions and resulting functional impairment of involved joints.

Although age (>40 years) was identified to be a strong risk factor for the development of OA, the role of biomechanical variables has taken on greater significance in recent years. Due to the growing prevalence of obesity, particularly

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Table 8.1 Symptoms of OA

• Pain
• Tenderness
• Swelling
• Deformation
• Articular effusion
• Limited range of motion

weight-associated hinge wear was found to act as a key mediator in the pathogenesis of degenerative joint diseases. A study by Must et al. (1999) has proved that "rates of knee osteoarthritis are remarkably higher among morbidly obese individuals than among individuals with normal weight (17 % vs. 10 %)". The role of obesity in the development of joint diseases is also demonstrated impressively by the fact that the incidence of OA is rising linearly with increasing BMI.

Corresponding studies performed by Bourne et al. (2007) revealed that "the probability of an obese patient requiring knee replacement increases with the degree of obesity measured according to the BMI (relative risk: 32.73-fold higher for people with body mass index >40 kg/m^2)".

Other risk factors associated with the development of OA include gender (female), previous traumatic joint injuries, weak thigh muscles and several sport disciplines (skiing, tennis, weight lifting, soccer, etc.) which are exerting strong mechanical stress on the joints. Metabolic disorders (gout, pseudogout) and inflammations (tendinitis, bursitis) may be further causes of joint problems (Fig. 8.1).

Early diagnosis and appropriate treatment of OA may be determining for the individual course of disease and are critical factors in the prevention of chronic morbidity among affected individuals. Changulani et al. (2008) have found that "increased knee pain and disability in morbidly obese patients (body mass index >40 kg/m^2) lead to knee replacement surgery at earlier ages than in individuals with normal weight (mean age difference: 13 years; $p = 0.001$)".

Therefore, patients who are at high risk for OA should carefully be interviewed and examined for any signs of joint deterioration. In case of abnormalities the diagnosis needs to be confirmed by the assistance of radiological imaging techniques. Morphological changes seen on X-ray include formation of osteophytes, joint space narrowing and subchondral bone sclerosis. Alternatively, conventional MRI can be used to assess the morphological integrity of the joint cartilage.

Subtle changes in joint cartilage microstructure require more sensitive imaging methods and may recently be detected by biochemical MRI, which registers minimal changes in the balance of water, chondrocytes, collagen fibres and protein molecules.

Depending on the radiological findings, sometimes arises the necessity for an additional diagnostic arthroscopy which allows an accurate assessment of cartilage breakdown. A commonly used grading system for chondral damage is the Outerbridge classification. It quantifies the severity of cartilage lesions with the assistance of four stages, starting from grades 0 to IV. 0 means normal cartilage, whereas grade IV describes a severe damage of chondral structures with exposed subchondral bone (Table 8.2).

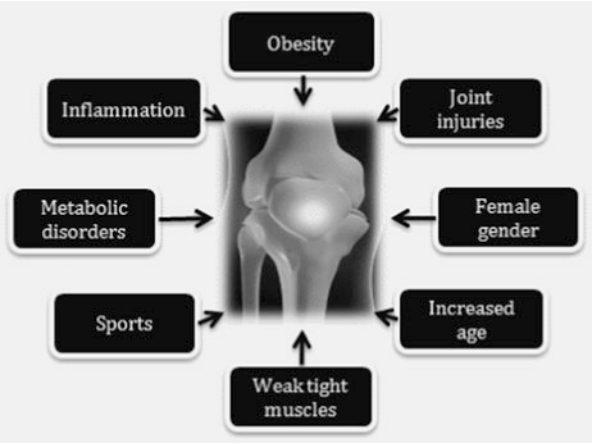

Fig. 8.1 Risk factors of OA

Table 8.2 Outerbridge classification

Grade 0	Normal
Grade I	Cartilage with softening and swelling
Grade II	Partial thickness defect with fissures on the surface that do not reach subchondral bone or exceed 1.5 cm in diameter
Grade III	Fissuring on the level of subchondral in an area with a diameter of more than 1.5 cm
Grade IV	Exposed subchondral bone

Today, OA is one of the leading causes for chronic disability and impairment among adults. In response to the growing prevalence of childhood obesity in developed as well as in developing countries increasing numbers of OA are expected in the near future. In 2001 it was estimated that 25 % of people aged over 55 are suffering from persistent knee pain (Peat et al. 2001).

Due to the lack of adequate treatment OA is associated with an extremely high economic burden for health insurance companies. A 2001 analysis on the total economic costs of OA and other rheumatic conditions in the USA registered annual expenditures of approximately $89.1 billion (Leigh et al. 2001). Consequently, the focus is on the implementation of risk-reducing strategies in order to control incidence rates of OA.

8.2 Pilot Study: Osteoarthritis in Morbidly Obese Adolescents

In response to the findings cited earlier, we conducted a pilot study at the Medical University of Vienna initiated in cooperation with the Centre for Joints and Cartilage (Department of Trauma Surgery) and the Division of Metabolism and

Nutrition (Department of Paediatrics and Adolescent Medicine) which is supposed to investigate the causes why subjects are complaining about pain in their knees, when they are getting overweight (Widhalm et al. 2012).

8.3 Methods

For this purpose 20 morbidly obese (>99.5 %) children and adolescents aged between 9 and 19 years (mean 14, 3 years) have been recruited and examined for symptoms of OA. The mean BMI was calculated to be 39.3 kg/m^2 ranging from 29 to 66 kg/m^2. All patients complained about knee pain, although none of them had a history of trauma.

The clinical evaluation involved a detailed anamnesis (nutrition, physical exercise) and physical examination. In the course of this procedure various clinical scores, the physical dimensions of the affected extremity and other anthropometrical data (height, weight, BMI) were assessed.

Radiological measurements were performed with X-rays of the painful knee. In addition to the standard X-rays in two planes (a.p., lateral), tangential pictures of the patella as well as long X-rays of the mechanical axis were made. Finally, conventional MRI (1.0 T) was used to visualize the morphological integrity of the joint cartilage. Due to the massive body circumference of the patients, the examination had to be conducted with an open MRI system.

8.4 Results

All patients examined in the study were indentified to have lesions of the cartilage which are varying in severity. Additional meniscal lesions could be found in 80 % of the participants.

Case Examples

Cartilage Lesion Grade IV

MRI of the knee performed on a 15-year-old morbidly obese male patient (Fig. 8.2).

The boy is complaining about severe knee pain over 2 years, whereas it was observed that the intensity of the pain was directly correlated with gaining weight. With a height of 168 cm the patient weights 170 kg which gives a corresponding BMI of 60.2 kg/m^2. The mean VAS score was 5 and the mobility of the knee was slightly reduced with a range of motion of 5-0-120. Image (a) presents a grade IV cartilage lesion in the lateral compartment of the joint. Further signs of OA could be found on image (b) which shows grade II and III cartilage lesions in the retropatellar region (Fig. 8.3, Table 8.3).

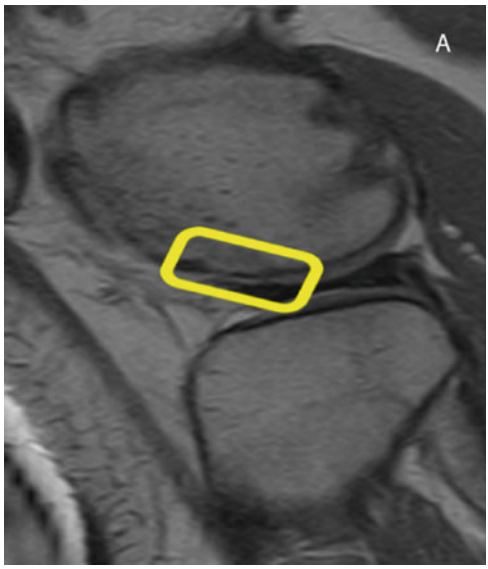

Fig. 8.2 Sagittal PDW-TSE, cartilage lesion grade IV on the lateral femoral condyle

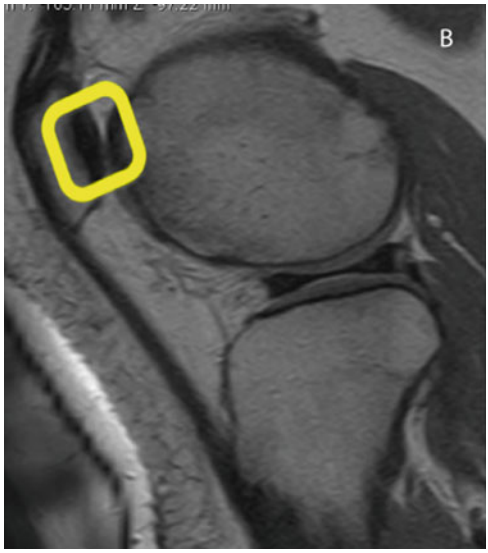

Fig. 8.3 Sagittal PDW-TSE, cartilage lesion grades II and III retropatellar

Table 8.3 15-year-old boy

Knee pain	
No trauma	
VAS	5
Height	168 cm
Weight	170 kg
BMI	60.2 kg/m^2
ROM	5-0-120

Table 8.4 11-year-old-boy

Knee pain	
No trauma	
Height	152 cm
Weight	66 kg
BMI	28.6 kg/m^2
ROM	0-0-145

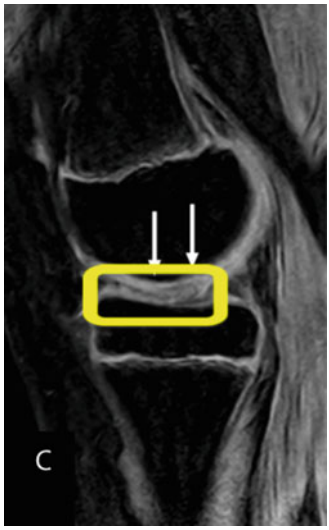

Fig. 8.4 Sagittal 3D WATS, cartilage lesion grades I and II medial compartment

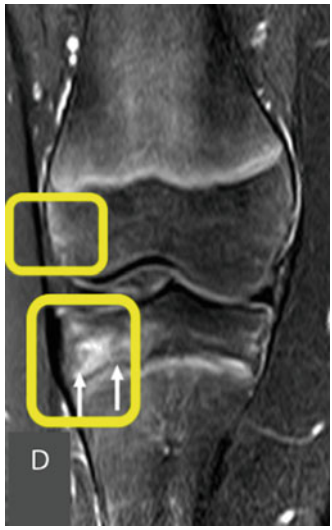

Fig. 8.5 Coronal PD TSE SPIR, bone bruise in the lateral femur condyle and tibia

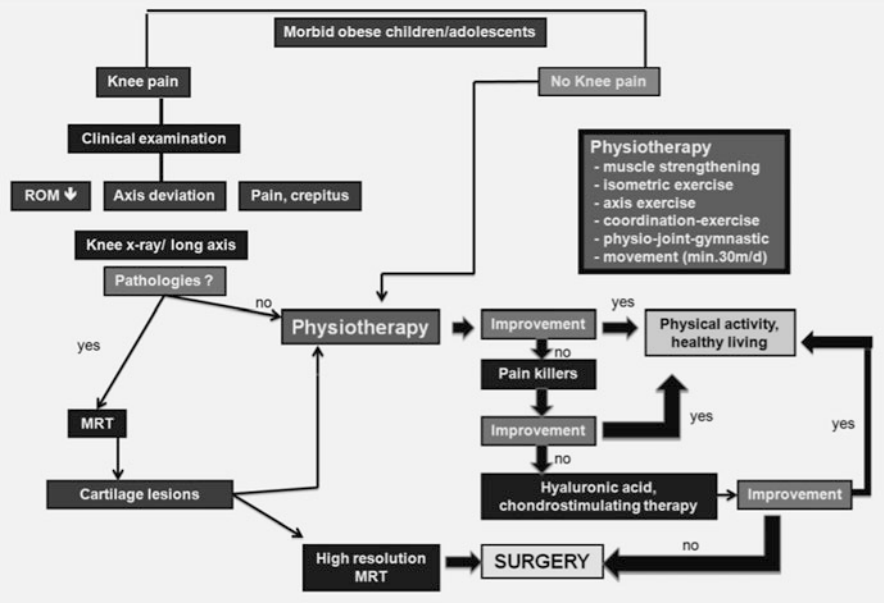

Fig. 8.6 Diagnosis and treatment concept

Cartilage Lesion Grade II

Sagittal 3D WATS (c) and coronal PD TSE SPIR (d)—MRI of an 11-year-old boy who is suffering from pain in his right knee without having any rememberable trauma. The patient is classified as morbidly obese with a height of 152 cm, a weight of 66 kg, and a corresponding BMI of 28.6 kg/m^2. Range of motion was assessed to be 0-0-145 in the affected joint (Table 8.4).

In image (c) cartilage lesions grades I and II according to the Outerbridge classification can be found in the medial compartment of the joint (white arrows) (Figs. 8.4 and 8.5).

An additional injury was identified in image d) and shows a bone bruise area in the lateral region of the tibia predominantly (white arrows).

The data collected in the course of this pilot study impressively demonstrate the significance of childhood obesity in the development of OA. Based on these results a concept for the diagnosis and treatment of knee joint injuries in morbidly obese adolescents was developed. The emphasis is on a precise clinical and radiological diagnosis to detect signs of beginning joint deterioration. In case of mild to moderate cartilage changes or missing pain a conservative treatment involving physiotherapy and pharmacological interventions should be considered. Severe cartilage lesions and the failure of conservative treatment approaches however, can be regarded as indications for a surgical correction (Fig. 8.6).

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Chapter 9
Bariatric Surgery in Adolescents: Practical Guidelines from a Pediatrician's Point of View

Kurt Widhalm and Oliver Helk

While morbid obesity is not a new phenomenon, the prevalence especially in the European- and US-American population drastically increased over the last three decades. Current prevalence of obesity (BMI > 30) in Europe is reported to be between 10 % and 20 % in men and 15–25 % in women. Approximately half of the European population is considered overweight or obese (BMI > 25) (James et al. 2004). Recent estimations forecast severe obesity prevalence of 11 % in the USA with an obesity prevalence of 42 %. More importantly, if the increase of the prevalence of obesity could be halted, 550 billion dollars could be saved in healthcare expenditures in the USA alone (Finkelstein et al. 2012). It is therefore of utmost importance to find cost-effective ways of treating (or even preventing) adiposity.

In most cases of severe obesity conservative means of treatment do not lead to adequate weight loss. As described in other chapters achieving long-lasting results with conservative treatment by nutritional means and physical activity is very difficult in these individuals due to severe eating disorders and danger of joint damage due to excessive weight. Unfortunately especially these patients who are often suffering from secondary diseases like hypertension, impaired glucose tolerance, or diabetes would profit the most from a fast and effective weight loss regimen—something that conservative methods can rarely provide. In these cases bariatric surgery becomes the method of choice.

The idea of performing metabolic surgery in obese adolescents is not a new one: first reports of bariatric procedures in pediatric age range back to 1971. In contrast to the technique itself the high case number in which surgery is performed is a rather new development and yet, to date of publication, there are still no broadly accepted guidelines on metabolic surgery in pediatric age. Existing recommendations for guidelines are to this point based on expert opinion rather than results from clinical trials due to a significant lack of long-term results. Many recommendations

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are based on data from adult studies. It can therefore be quite difficult for the clinical practitioner faced with the problem of morbidly obese adolescent patients to decide when the possibility of referring the patient to a bariatric procedure in a specialized center should be discussed.

The following guidelines are internationally published:

1. IPEG Guidelines for Surgical Treatment of Extremely Obese Adolescents (IPEG Guidelines, J Laparoendosc Adv Surg Tech). The IPEG recommends a BMI of >35 kg/m^2 with severe obesity-related comorbidities or a BMI of >40 kg/m^2 with less severe comorbidities as inclusion criteria for bariatric surgery. Severe comorbidities are defined as Type 2 diabetes mellitus, moderate or severe obstructive sleep apnea (AHI >14 events/h), and pseudotumor cerebri). In regard to the minimal age in which surgery should be performed the IPEG requires the patient to have or have nearly reached adult stature (e.g., >95 %). Psychological evaluation in regard to family function and other traits possibly influencing the postoperative regimen adherence and most importantly assessment of the patient's psychological maturity is strongly recommended. Exclusion criteria are defined as substance abuse problems in the preceding year, the presence of a psychiatric diagnosis possibly affecting adherence to postsurgical therapy, a medically correctable cause for obesity (such as Morbus Cushing), inability of the patient to fully comprehend the consequences of the procedure, and the clear inability or refusal to participate in lifelong follow-up. Caution, but not necessarily exclusion, is recommended when facing a history of poorly documented weight loss attempts, drastic behavioral problems present throughout adolescence, lack of realistic expectations, and/or a history of poor compliance with other medical treatments. In regard to the most practicable technique the IPEG does not give any recommendations but states that gastric banding, sleeve gastrectomy, and gastric bypass are all valid options. Concerning the postsurgical follow-up the recommendations consist of weekly visits in the first month, monthly visits in the first 3 months, and then quarterly visits with the surgeon, dietician, psychologist, and exercise physiologist in order to identify possible complications and to reinforce compliance. The patient is recommended to consume at least 60–70 g of lean protein per day as well as multivitamin supplementation. Furthermore calcium, vitamin B1, and vitamin B12 should be added after gastric bypass procedures. Additionally female patients should be provided with iron supplementation.
2. Intradisciplinary European Guidelines for Surgery for Severe (Morbid) Obesity (Intradisciplinary European Guidelines). These guidelines clearly state that bariatric surgery in adolescents should only be considered in centers with extensive experience with such procedures in adults and which are able to offer a multidisciplinary approach with pediatricians, dieticians, and psychologists involved. Inclusion criteria involve a BMI >40 or >99.5th percentile for respective age, at least one comorbidity, a history of at least 6–12 months of conservative weight reduction attempts in a specialized center, skeletal and developmental maturity, the ability to participate in a postoperative

multidisciplinary treatment program, and the ability to commit to comprehensive medical and psychological assessment before and after surgery. There is a clear statement that bariatric surgery can furthermore be considered in patients affected with genetic syndromes (e.g., Prader–Willi Syndrome) after careful consideration of an expert pediatric and surgical team. Contraindications include absence of periods of identifiable medical management, inability to participate in long-term follow-up, non-stabilized mental disorders, substance abuse, diseases threatening life in the short term, and a patient unable to care for himself with no or insufficient family or social support. Preoperative evaluation of the patient should ideally be performed by a physician/pediatrician, a surgeon, an anaesthetist, a psychologist and/or psychiatrist, and a nurse practitioner and/or social worker. The following measurements are recommended in addition to routine preoperative assessment as for any other major abdominal surgery: Pulmonary function and diagnosis of sleep apnea syndrome, metabolic and endocrine disorders, gastroesophageal disorders, body composition, bone density measurement, and indirect calorimetry. Adjustable gastric banding, Vertical banded gastroplasty, gastric bypass, and biliopancreatic diversion with and without duodenal switch are listed as valid surgical procedures with increasing expectable weight loss in chronological order. On the other hand, however, it is clearly stated that long-term risk for micronutrient deficiency and other metabolic complications increase as well. The decision should be made for each patient individually with special regard to the surgeon's experience. The follow-up routine should be adjusted to the procedure performed: for adjustable gastric banding, vertical banded gastroplasty, and other pure gastric restrictive operations quarterly visits starting 1 month post-surgery during the first year are recommended with yearly visits thereafter. Concerning gastric bypass and biliopancreatic diversion the guidelines are stricter with a checkup after 1 month, a follow-up of at least every three months during the first year, visits every 6 months in the second year, and annual visits thereafter. Vitamin and micronutrient supplementation should be routinely prescribed as a preventive regimen. If deficits are found manifest in patients after biliopancreatic diversion, supplementation should be administered parenterally.

3. ANZ Guidelines and recommendations (Dixon et al. 2011; Baur and Fitzgerald 2001). The ANZ recommends bariatric surgery to be performed only in adolescents of at least 15 years of age with the possibility to include patients of 14 years in not nearer defined exceptional circumstances. In these guidelines, bariatric surgery is explicitly considered a possible treatment for only a minority of severely obese adolescents. Adequate skeletal and sexual maturity is necessary. Patients need to have a BMI >40 or alternatively >35 kg/m^2 with severe comorbidities such as diabetes mellitus type II, hypertension, nonalcoholic steatosis hepatitis, obstructive sleep apnea, and pseudotumor cerebri. A history of at least 6 months of unsuccessful conservative weight loss attempts in a supervised, multidisciplinary manner is required as well as the patient's ability for informed consent and understanding all consequences of surgery. In contrast to the European guidelines, genetic syndromes like Prader–Willi are considered an exclusion criterion. Further exclusion criteria consist of untreated or

untreatable psychiatric or psychological disorders, pregnancy or breastfeeding, and significant cognitive impairment. The ANZ guidelines strongly recommend that all adolescent patients undergoing bariatric surgery should participate in a study of the outcomes. The establishment of a national register for bariatric patients is furthermore endorsed. Preoperative assessment should consist of evaluation of the adolescents' general health and developmental status, the patient's and family's motivation and expectation, their knowledge of the procedure and postoperative requirements, their capacity for self-care, and an evaluation of obesity-related comorbidities. These assessments should ideally be undertaken by a multidisciplinary team with a special focus to an accredited practicing dietician. In contrast to the other guidelines, the ANZ recommends the laparoscopic adjustable gastric banding as the method of choice. No clear follow-up program is proposed, but the need of development of such is mentioned. However, it is strongly recommended to conduct a lifelong follow-up in a multidisciplinary manner.

4. The US-American work group of Pratt et al. recommends a Tanner stage of IV or V as eligibility criteria for bariatric surgery. Exceptions can be made if severe comorbidities demand surgical intervention at an earlier stage. A skeletal maturity of at least 95 % is demanded if a malabsorptive procedure is planned. The BMI cut-point in children and adolescents is recommended to be >35 with major comorbidities (defined as type 2 diabetes, severe sleep apnea, pseudotumor cerebri, or severe NASH) or >40 with at least one comorbidity (e.g., hypertension, insulin resistance, dyslipidemia, mild sleep apnea, impaired quality of life). For patients with syndromatic obesity decision for surgery should be made on a case-by-case basis. The patient needs to demonstrate the ability to understand the changes in diet and physical activity required for optimal postoperative outcomes. There needs to be evidence for mature decision making with appropriate understanding of the potential risks and benefits. Exceptions can be made for individuals with mental retardation—for these cases decisions should be made on a case-by-case basis. In such cases the inclusion of an ethicist is recommended. Appropriate social and familial support are also requirements which need to be met. Pratt et al. suggest gastric bypass as surgery technique of choice as long as long-term follow-up is provided. Gastric banding and sleeve are both only recommended in clinical trials. BPD and duodenal switch are not recommended under any circumstances to the high risk of protein malnutrition, bone loss, and micronutrient deficiencies. Bariatric surgery in adolescents should only be performed with the use of a multidisciplinary team of at least four to five professionals who are co-located and have at least one face-to-face meeting preoperatively with the patient. Primary team members should include a surgeon, a pediatrician, a dietician, a mental health specialist, and a coordinator. The bariatric center for weight loss surgery in adolescents and/or children should ideally be co-located with an adult weight loss surgery program to allow for share of equipment and experience. Roux-en-Y gastric bypass is recommended as the method of choice while gastric banding and sleeve should be considered investigational. BPD is not recommended due to the increased risk of nutrient deficiencies.

Source of guidelines	Inclusion criteria	Exclusion criteria	Surgical method of choice	Recommendations for follow-up	Recommendations for supplementation
IPEG	BMI of >35 kg/m^2 with severe obesity-related comorbidities or a BMI of >40 kg/m^2 Severe comorbidities: DM II, moderate or severe obstructive sleep apnea (AHI >14 events/h), pseudotumor cerebri, >95 % skeletal maturity	Substance abuse problems, psychiatric diagnosis possibly affecting adherence to postsurgical therapy, medically correctable cause for obesity, obvious inability to comply in lifelong follow-up	Gastric banding, sleeve gastrectomy, gastric bypass	Weekly visits in the first month, monthly visits in the first 3 months, and then quarterly visits with the surgeon, dietician, psychologist, and exercise physiologist in order to identify possible complications and to reinforce compliance	60–70 g of lean protein per day as well as multivitamin supplementation. Calcium, vitamin B1, and vitamin B12 should be added after gastric bypass procedures. Additionally female patients should be provided with iron supplementation
European Guidelines (IFSO)	BMI >40 or >99.5th percentile for respective age, at least one comorbidity, a history of at least 6–12 months of conservative weight reduction attempts in a specialized center, skeletal and developmental maturity, the ability to participate in a postoperative multidisciplinary treatment program, syndromatic obesity	Absence of periods of identifiable medical management, inability to participate in long-term follow-up, non-stabilized mental disorders, substance abuse, diseases threatening life in the short term, and a patient unable to care for himself with no or insufficient family or social support	Adjustable gastric banding, vertical banded gastroplasty, gastric bypass, biliopancreatic diversion	For purely restrictive operations quarterly visits starting 1 month postsurgery during the first year and yearly visits thereafter. Gastric bypass and biliopancreatic diversion: checkup after 1 month, a follow-up of at least every 3 months during the first year, visits every 6 months in the second year, and annual visits thereafter	Vitamin and micronutrient supplementation should be routinely prescribed as a preventive regimen. If deficits are found manifest in patients after biliopancreatic diversion, supplementation should be administered parenterally

(continued)

Source of guidelines	Inclusion criteria	Exclusion criteria	Surgical method of choice	Recommendations for follow-up	Recommendations for supplementation
ANZ Guidelines	At least 15 years of age. Adequate skeletal and sexual maturity is necessary. BMI >40 or alternatively >35 kg/m^2 with severe comorbidities (DM II, hypertension, nonalcoholic steatosis hepatitis, obstructive sleep apnea, and pseudotumor cerebri. A history of at least 6 months of unsuccessful conservative weight loss attempts	Genetic syndromes like Prader–Willi are considered an exclusion criterion. Further exclusion criteria consist of untreated or untreatable psychiatric or psychological disorders, pregnancy or breastfeeding, and significant cognitive impairment	Laparoscopic adjustable gastric banding	Strong recommendation for lifelong follow-up, no clear procedure stated	No recommendations stated
US work group (Pratt et al.)	Skeletal maturity of at least 95 % (malabsorptive procedure), BMI >35 with major comorbidities (DMII, severe sleep apnea, pseudotumor cerebri, or severe NASH) or >40 with at least one comorbidity (e.g., hypertension, insulin resistance, dyslipidemia, mild sleep apnea, impaired quality of life)	Inadequate family and social support	Gastric bypass	Not stated	Not stated

9.1 Conclusion

Recommendations for weight loss procedures vary greatly between the different continents. This fact clearly shows the need for a global consensus. Over all, gastric bypass appears to be a valid procedure for all involved work groups and there is largely a consensus concerning the need of appropriate follow-up and supplementation. In any case, bariatric surgery should be considered as an option for only a minority of obese individuals and only when conservative methods have failed.

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Chapter 10
Vitamin Deficiencies After Bariatric Surgery?

Oliver Helk and Kurt Widhalm

10.1 Nutritional Problems Associated with Bariatric Surgery

Although complication rates of bariatric surgery in itself are rather low when performed in specialized centers, there is a possibility for side effects in the follow-up. Patients after bariatric surgery have a tendency of showing poor treatment- and follow-up adherence and micronutrient deficiencies can occur. Deficiencies of micronutrients before and after Bariatric surgery are not well studied but are nonetheless a very important issue in order to prevent adverse effects caused by dramatically changed eating habits. Strict long-term follow-up is necessary in order to identify such deficiencies, and further results are needed to provide guidelines for optimal micronutrient supplementation after surgical procedures for weight reduction.

The next paragraphs aim to review current literature on possible and reported micronutrient deficiencies in adults. To date of publication, not a single paper dealing with micronutrient deficiencies in adolescents could be found.

10.1.1 Thiamin (Vitamin B_1)

The most drastic complication of a Vitamin B1 deficiency is Wernicke Encephalopathy, leading to symptoms such as ataxia, psychosis, mental confusion, and opthalmoplegia. Patients with persistent vomiting after surgery and/or rapid weight loss are at increased risk. Underprovision rates in gastric bypass patients are reported to be up to 49 % (Aasheim et al. 2009a) with further increased risk in

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patients who underwent a doudenal switch (Lakhani et al. 2008). Thiamin deficiency has been reported in bariatric surgery patients who experience persistent vomiting, inadequate dietary intake, and rapid weight loss. Recommendations for postsurgical provision in order to prevent deficiencies range from 50 mg/day of oral supplementation (Davies et al. 2007) to prophylactic parenteral administration (Loh et al. 2004). It is important to note that the symptoms of Vitamin B1 deficiency are in some cases misinterpreted as symptoms of hypoglycemia. If glucose is administered without thiamin this can further worsen the cytotoxicity to the brain (Loh et al. 2004).

Vitamin B1 deficiencies have been reported to manifest after approximately 6 weeks after surgery (Bernert et al. 2007).

10.1.2 Folate (Vitamin B9)

Prevention of folate deficiencies are of especially high importance in female patients in the birth-giving age. Due to the fact that these patients show an increased rate of pregnancy after a bariatric procedure, this aspect deserved special attention. Adequate folate provision is necessary for normal neural tube development in the unborn child.

Potential manifestations of a folate deficiency involve leucopenia, thrombocytopenia, elevated homocysteine levels, and megaloblastic anemia (Decker et al. 2007; Malone 2008). Folate deficiencies seem to occur rarely; however, there are reports of deficiency rates of 38 % after gastric bypass (Halverson 1986). A daily oral supplementation of 1 mg appears to be sufficient to prevent underprovision in most patients (Kushner 2000; Boylan et al. 1988).

10.1.3 Cyanocobalamin (Vitamin B_{12})

Vitamin B12 needs to be substituted in all patients who underwent any procedure apart from Gastric Banding due to the disconnection of large parts of the curvatura major from the digestive tract. The resulting lack of intrinsic factor can therefore lead to severe malabsorption (Vargas-Ruiz et al. 2008). Bacterial overgrowth in the disconnected ilium (due to lack of digestive enzymes) resulting in increased consumption of Vitamin B12 may also be a possible reason (Oxentenko and Litin 2009). A Vitamin B12 deficiency can manifest in the form of leucopenia, macrocytic anemia, thrombocytopenia, and paresthesia or other neurological symptoms (Feit et al. 1982; MacLean 1982; Bukoff and Carlson 1981).

Published suggestions for routinely prescribed supplementation range from 350 µg/day (Rhode et al. 1995) to 2,000 µg/day (Butler et al. 2006). Supplementation can be administered orally or parenterally; however, much higher doses are needed in oral supplementation.

10.1.4 Ascorbic Acid (Vitamin C)

To date of publication, only two reports are available in which Vitamin C was assessed. Deficiency rates differ between these articles from 0 % to 35 % (Clements et al. 2006; Aasheim et al. 2009b). Symptoms include poor wound healing, gingivitis, glossitis, and petechiae. In severe cases scurvy can occur.

10.2 Fat-Soluble Vitamins

Production of lipolytic enzymes is reduced after malabsorptive procedures due to impairment of cholecystokinin stimulation. This leads to delayed lipid digestion and malabsorption of fat soluble vitamins. In contrast to water-soluble vitamins, in which deficiencies usually occur early after surgery, deficiencies of the Vitamins A, D, E, K develop slower and after a longer period of time (Schweitzer and Posthuma 2008).

10.2.1 Vitamin A (Retinol)

Reported rates of Vitamin A deficiencies range from 11 % (multivitamin supplementation) (Clements et al. 2006) to 69 % (no supplementation specified) (Slater et al. 2004) in gastric bypass patients. Symptoms of a Vitamin A deficiency include tiredness, nausea, hair loss, and in severe cases xeropthalmia and night blindness. The prescription of 2,500 IU daily in addition to multivitamin substitution is suggested by one group (Davies et al. 2007; Hatizifotis et al. 2003).

10.2.2 Vitamin D and Calcium

Since Vitamin D is an essential hormone in bone metabolism and therefore plays a major role in skeletal growth, it appears logical that prevention of deficiencies has an even greater importance in adolescents than in adults (Pournaras and Le Roux 2009). However, it is worth mentioning that so far no data concerning the possible effects of Vitamin D deficiencies exists. Vitamin D is needed for both skeletal and extraskeletal functions including immune function, cancer prevention, and cardiovascular health (Khazai et al. 2008). Most of the candidates for bariatric surgery are were not consuming sufficient amounts of Vitamin D prior to surgery (Bloomberg et al. 2005). Ammor et al. (2009) reported that the majority of candidates for gastric bypass surgery were not consuming recommended amounts of Vitamin D prior to surgery. Preexisting deficiencies can be further worsened after surgery due to

limited food intake and the bypassing of the primary Vitamin D and Calcium resorption sites (duodenom, jejunum).

In gastric bypass patients, incidence of calcium and Vitamin D deficiency was indicated to be increased significantly with the length of the Roux-en-Y limb (Gasteyger et al. 2008). This leads to an increased rate of bone demineralization by elevated bone resorption which goes hand in hand with higher risk for fractures (Slater et al. 2004; Goode et al. 2004).

Recommendations concerning the supplementation of calcium and Vitamin D to prevent bone loss in patients after bariatric surgery vary (Clements et al. 2008; Davies et al. 2007). The citrate form of calcium is assumed to be more effective than carbonate salts because citrate can be absorbed easier in absence of stomach acid (Alvarez-Leite 2004; Tondapu et al. 2009). Recommended Calcium citrate doses are ranging from 0.5 to 1.5 g/day. Vitamin D dosage recommendations range from 400 to 800 IU/day. Other studies recommend the use higher doses of Vitamin D after gastric bypass (Carlin et al. 2009; Goldner et al. 2009). A single work group evaluated Vitamin D supplementation at 800; 2,000; and 5,000 IU/day in gastric bypass patients. 5,000 IU resulted in the best improvement of serum 25-hydroxy Vitamin D and did not cause any cases of hypercalcemia (Goldner et al. 2009).

10.2.3 Vitamin E

Studies on Vitamin E deficiencies in bariatric patients are rare. Symptomatic deficiencies appear to be uncommon. 4–10 % of bariatric patients have been found to have low serum Vitamin E levels after surgery, but no symptoms or complications were reported (Boylan et al. 1988; Slater et al. 2004; Dolan et al. 2004). A supplementation of 10 mg/day Vitamin E is recommended (Davies et al. 2007).

10.2.4 Vitamin K

A single study reported that 3 years after gastric bypass, 50 % of subjects had low, but asymptomatic plasma levels of Vitamin K (Diniz Mde et al. 2004). A supplementation dose of 25 μg/day of Vitamin K is recommended (Davies et al. 2007).

10.3 Deficiency of Trace Minerals

Several trace element deficiencies have been identified after bariatric surgery, as the main sites of nutrient absorption are bypassed.

10.3.1 Iron

Iron (Fe) deficiency is common in bariatric patients (especially in females) and can be seen as the most common cause of anemia in this collective. Copper can cause anemia as well and should also be considered. For menstruating women an additional supplementation of two 320 mg ferrous sulfate capsules per day is recommended (Mizon et al. 2007). Resorption of iron is hindered in bariatric patients due to reduced production of HCl in the stomach and bypassing of the primary resporption sites (duodenum, jejunum) (Halverson 1986; Mizon et al. 2007). Taking Fe supplements in combination with Vitamin C will enhance absorption (Decker et al. 2007).

10.3.2 Selenium

Selenium (Se) can occur in 14–22 % of postbariatric surgery patients (Lapointe-Gagne and Gagner 2005; Prodan et al. 2009) and can lead to cardiomyopathy. Other symptoms include peripheral muscle involvement (myositis), weakness, cramps, and hypothyreosis. Daily supplementation of 50 μg is recommended (Clements et al. 2008).

10.3.3 Zinc

The lead symptom of Zinc deficiency is significant hair loss. Other complications include psychic disorders, higher rates of infections, and diarrhea. An additional supplementation of 6.5 mg/day is endorsed (Davies et al. 2007).

10.3.4 Copper

Copper deficiency can lead to hematologic and neurologic symptoms. Anemia (normocytic) and myeloneuropathy can be considered the most common (Prodan et al. 2009; Juhasz-Pocsine et al. 2007). No studies on copper levels after bariatric surgery are available; however, some case reports show that the occurrence of symptoms from copper deficiency is possible in bariatric patients (Prodan et al. 2009). No general supplementation is recommended. Medical experts should be vigilant for neurologic and hematologic symptoms and should, in such cases, consider the possibility of copper deficiencies.

Table 10.1 Recommendations for additional supplementation after the different types of bariatric surgery

Micronutrients	Recommended dietary allowances	Banding, gastric bypass, and sleeve resection (Additional % of RDA)
Vitamin A	900 μg RAE (3,000 IU)	100
Vitamin B_1	1.1–1.3 mg	150
Vitamin B_{12}	2.4 μg	300
Folic acid	400 μg	150
Vitamin C	75–90 mg	200
Vitamin D	5 μg (200 IU)	200
Vitamin E	15 mg	100
Vitamin K	150 μg	25
Copper	900 μg	50
Iron	8–18 mg	50
Selenium	55 μg	50
Zinc	8–11 mg	50

10.3.5 Other Essential Trace Elements

There are no reports of manganese or chromium deficiencies after bariatric surgery.

10.4 General and Medical Nutrition Therapy Recommendations

As appropriate laboratory tests for deficiencies have limitations and can be considered as quite expensive, it is important to do "as much as needed, as little as possible." Additionally, many obese patients show preexisting deficiencies before surgery. Therefore micronutrient assessment should be done preoperatively. All patients scheduled for bariatric surgery should receive daily multivitamin and multi-trace mineral supplements (Pournaras and Le Roux 2009). Serum 25-hydroxy Vitamin D levels are available in most laboratories and should be done accordingly. An elevation of prothrombin time implies Vitamin K deficiency, although a normal level does not rule out a subclinical deficiency. Serum levels of Vitamins C, B_{12}, and folate should be obtained. Thiamin levels are not easily available and are not necessary as prophylactic thiamin administration is safe and inexpensive.

Current recommendations concerning the time at which follow-up should be done state blood sampling 3, 6, 12, and 24 months after surgery (Pournaras and Le Roux 2009). In Table 10.1 the Recommended Dietary Allowances of different micronutrients as well as recommended supplementation doses for bariatric patients are given (Sriram and Lonchyna 2009; Davies et al. 2007; Pournaras and Le Roux 2009). Administering marginally too high amounts of vitamins (especially

when water-soluble) has no clinical consequence. Therefore, when the recommended dosages cannot be met exactly, we suggest to administer the higher amount.

Vitamin deficiencies in female patients require special attention due to increased rate of pregnancies after bariatric surgery. Close monitoring of such individuals is necessary in order to prevent damage to the unborn child (Guelinckx et al. 2009).

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Chapter 11
Laparoscopic Gastric Banding

Karl Miller

11.1 Introduction

Weight change has traditionally been used as the primary outcome in obesity intervention studies (Treadwell et al. 2008). Increasing evidence suggests that traditional nonsurgical weight loss methods are ineffective and that bariatric surgery is the most sustainable and effective treatment for weight loss in the morbidly obese (O'Brien et al. 2010; Dolan et al. 2003; Dillard et al. 2007; Nadler et al. 2008). Comorbidities associated with severe obesity in childhood are found in up to 50 % (Weiss et al. 2004). Presently, the most common surgical options for adolescents are Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding (LAGB). LAGB is associated with a lower mortality rate and threefold lower complication rate than gastric bypass (Inge et al. 2007; Xanthakos 2008), has the advantages of adjustability and reversibility, and has been associated with sustained weight loss and improved comorbidities in adults (O'Brien et al. 2006).

11.1.1 Development of the Laparoscopic Gastric Band (LAGB)

In 1978, Wilkinson pioneered the concept of gastric banding in an open procedure by surrounding, and thus constricting, the upper stomach with a 2-cm-wide nonadjustable mesh fabric (Marlex®) (Wilkinson and Peloso 1981), an innovation that was ineffective in achieving sufficient weight loss and which were, unfortunately, also associated with high rates of reoperation, as the stomach tissue

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stretched postoperatively and the stoma diameter of the band could not be modulated (Buchwald and Buchwald 2002; Vasallo et al. 2002).

In a 1984 meeting presentation and 1989 report, Szinicz and Muller (1984) and Szinicz et al. (1989) presented the results of their experiments in minipigs implanting a "reversible" gastric band, the forerunner of today's adjustable gastric bands.

Hallberg and Forsell published their first report of an *adjustable* gastric band in 1985 in Huddinge University Hospital, Sweden. In 1993, Belachew et al. reported their animal studies of laparoscopic placement of the adjustable band, and in 1994 and 1995, Belachew et al. and, in 1997, Forsell et al. reported performing the first human implantations of *laparoscopic adjustable* gastric bands (generically, "LAGBs"). Belachew et al. employed a "perigastric" technique, Forsell et al., the "pars flaccida" technique.

11.2 The LAGB System

The adjustable band is placed around the upper part of the stomach, leaving a small section of stomach (about 10–15 mL) above the band; the main part of the stomach lies below the band. A small passage is left open through the section of stomach surrounded by the band, so that liquids and food can still flow through from the upper to the lower part of the stomach.

The adjustable gastric band allows the surgeon to modify the width of the opening of the stoma by injecting or removing liquid from the inflatable balloon that is fixed to the inside of the band. The balloon portion of the band is attached to a long tube that plugs into an injection port. The injection port is fixed to the stomach muscle during the operation and can be localized by X-ray or palpation later (Fig. 11.1).

The surgeon can remove or add liquid to the balloon of the band via the injection port, thus altering the inner diameter of the closed band: more liquid in the balloon will reduce the opening of the stoma, whereas by removing liquid from the balloon, the opening will increase, enabling more food to pass through into the stomach.

This procedure of adjustments can be done on an out clinic basis according to each patient's need without a further surgery. The surgery could be performed on a day case basis (Cobourn et al. 2010) or a hospital stay of 1–2 days.

11.3 Indication and Patient Selection

In 2004 first Inge and Wittgrove et al. on behalf of the American Society for Metabolic and Bariatric Surgery (ASMBS 2004) outlined indications for surgery. In 2007 the interdisciplinary European guidelines for bariatric surgery (Fried et al. 2007) were established, defining the criteria for adolescent patients as well

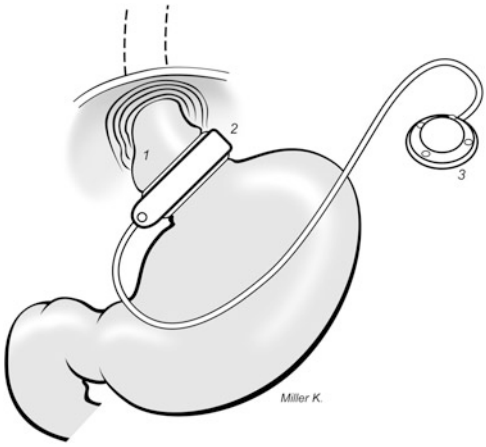

Fig. 11.1 Laparoscopic adjustable gastric banding (LAGB) system. (1) Stomach pouch (approx 10–15 mL) for early satiety, (2) LAGB, (3) and port system for band adjustment

Table 11.1 Indication according to Inge et al. (2004) and Wittgrove (2004) and the Interdisciplinary European Guidelines (Fried et al. 2007)

• Severely obese adolescents (above the 99.5th age- and gender-adjusted growing percentile)
• Intervention tailored individual to bypass or banding
• Multidisciplinary team (pediatritian, psychologist, nutritionist/dietitian)
• Nutrition and physical activity
• Understand risks and side effects
• Highly trained and skilled bariatric surgeons
• Standardized perioperative including follow-up program
• Less than 14 years of age with at least one comorbidity

(Table 11.1). According to the interdisciplinary European guidelines for bariatric surgery, patients above the 99.5th age- and gender-adjusted growing percentile were considered for surgical treatment. In addition, adolescents of less than 14 years old had to suffer from at least one comorbidity (Fried et al. 2007). Special attention was directed at the psychological evaluation and involvement of the adolescents' families because of the necessity to change eating habits and lifestyle. Prior to surgery, all patients should be evaluated by a multidisciplinary team consisting of pediatricians, endocrinologists, dietitians, psychologists, and bariatric surgeons. Patients must have failed to reduce and maintain weight loss through several methods such as diet camps and/or behavioral therapy. Additionally, these patients were evaluated for their compliance. Preoperative evaluation included metabolic screening and routine blood chemistry workup and should be screened for comorbidities. Additionally anthropometric data such as waist-to-hip ratio and the glucose disposition index blood pressure measurements should be performed routinely in all patients.

The inclusion of psychological scales in pretreatment diagnosis and follow-up is supported by new findings suggesting that individual characteristics, such as the degree of dietary restraint and internalizing psychopathology, can be useful in

classifying overweight children and adolescents, stipulating specific treatment guidelines, and making differential prognoses (Braet and Beyers 2009).

Based on the Interdisciplinary test system for diagnosis and evaluation of obesity (Ardelt-Gattinger and Meindl 2010) we highly recommend the Bariatric Evaluation Score for Children (BAREV-C). The BAREV-C is the first comprehensive outcome instrument for pre/post intervention evaluation of obese individual children as well as groups. It can be applied for intervention studies but also provides the clinician with a differentiated overview in daily practice (Weghuber et al. 2013).

11.4 Follow-Up and Band Adjustments

Postoperatively, adolescents, children, and their families must receive psychological and dietary support. We perform the first calibration of the band not before 4–6 weeks after surgery. The patients have to visit the surgical outpatient clinic 3, 6, and 12 months after surgery and afterwards every 6 months. The follow-up examinations include measurement of body weight, blood pressure, nutrition and eating behavior instruction, and the Quality of Life Questionaire (Moorehead et al. 2003) to analyze psychological changes. This form was extended by excessive weight loss and improvement of medical conditions to the Bariatric Analysis and Reporting Outcome System (BAROS) which was described in 1998 by Oria.

The LAGB should be adjusted in an optimal zone of early satiety and fullness which needs sometimes several visits and fillings to find. Vomiting and regurgitations are absolutely to avoid and could lead to complications which are described in the results.

11.5 Results

Randomized controlled trials involving adults have shown gastric banding to be more effective and cost-effective than optimal lifestyle treatment (O'Brien et al. 2006; Dixon et al. 2008; Keating et al. 2009). Gastric banding has been proposed for treating obese adolescents in a systematic review of bariatric surgery (Treadwell et al. 2008).

The first randomized controlled trial from O'Brian published in 2010 of treatment with the gastric banding procedure vs. a lifestyle weight loss program for adolescents with severe obesity showed that weight measures and health status improved in both study groups. However, the extent of the weight loss was substantially greater for those in the gastric banding group, which also showed improvement in health with complete resolution of the metabolic syndrome and insulin resistance and quality of life measurement. A systematic review of gastric banding for treating obese adolescents is summarized in Table 11.2. LAGB for adolescents and children in experienced centers is a safe procedure where

Table 11.2 Studies of adjustable gastric banding in adolescents and children

Author/number	Age	BMI	Weight loss	Complications	Mortality	Follow-up
Angrisani et al. (2005) $N = 69$	15–19	46.1	39.7–55.6 % EWL	10.3 %	0 %	7 years
Conroy et al. (2011) $N = 45$[a]	NA	NA	25.9 EWL	NA	0 %	12 months
Horgan et al. (2005) $N = 54$	17–19	51	15–87 % EWL	NA	0 %	4–30 months
Nadler et al. (2007) $N = 53$	13–17	47.6	37–63 % EWL	9.4 %	0 %	6–24 months
Silberhumer et al. (2011) $N = 50$	9–19	45.2	92 % EWL	12 %	0 %	7 years
Widhalm et al. (2011) $N = 8$	16.9	49	20 ± 6.3 kg	0 %[b]	0 %	24 month
Yitzhak et al. (2006) $N = 60$	9–18	43	BMI 43 to 30	10 %	0 %	3 years

[a]Eligible for follow-up of 12 months
[b]4 out 8 had weight gain and conversion to gastric bypass
NA Not addressed

postoperative complications such as band slippage, esophageal dilatation, or band erosion on a long-term follow-up are rare (Angrisani et al. 2005; Silberhumer et al. 2011) and postoperative weight loss is comparable or even superior to that in adults (Inge et al. 2007; Fielding and Duncombe 2005). Patients with insufficient weight loss or weight gain could be converted to a gastric bypass procedure (Widhalm et al. 2011).

11.6 Discussion and Considerations

Bariatric surgery is now extensively used for adults and is being evaluated for adolescents in the interdisciplinary European guidelines on surgery of severe obesity [Fried et al. 2007]. The most common procedures are laparoscopic adjustable gastric banding (gastric banding) and Roux-en-Y gastric bypass (gastric bypass) surgery. Barlow SE noted in pediatrics: "Obesity in children and adolescents represents one of the most frustrating and difficult diseases to treat."

Most studies demonstrate that LAGB is an effective and safe procedure in a very carefully selected and multidisciplinary team treated patient population. Within the context of academic medical centers, adolescent bariatric surgery is associated with low morbidity and no mortality. The attractiveness of this procedure as first-line surgical treatment in a multidisciplinary setting is due to the reversibility of the

procedure without altering the physiological intestinal tract in a very dynamic patient population. Significant weight loss is usually observed during the first 3 years after treatment and decreases thereafter, which correlates with the observed improvement in quality of life. When the treatment fails, gastric bypass procedure should be offered as an early alternative second-line treatment.

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Chapter 12
Metabolic Surgery in Adolescents

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12.1 Introduction

Obesity is the biggest epidemic challenge of the twenty-first century. As a consequence of its subsequent comorbidities like diabetes, various types of cancer, and cardiovascular disease, it shortens life expectancy dramatically. Beside bariatric surgery, there is no conservative treatment modality achieving maintainable and sustained weight loss in morbidly obese patients. In the course of evolving weight loss surgery procedures, more and more positive effects have been emerging on metabolism, especially diabetes. This led to the new term "metabolic surgery" instead of "bariatric surgery," reflecting that surgical intervention on obesity is not limited to weight loss itself anymore but also directly improves several metabolic disorders.

All these facts also apply to adolescents: Obesity is no longer an adult disease (Stefater et al. 2012). Many recent publications document the rapid and alarming increase of BMI, overweight, and obesity in adolescents (Flegal et al. 2010; Ogden et al. 2010; Flodmark et al. 2004; Michalsky et al. 2012; Poglitsch et al. 2011; Dietz 2004) not only in the USA (Flegal et al. 2010; Ogden et al. 2010) but also Europe (Flodmark et al. 2004; Livingstone 2000; Kipping et al. 2008) and other parts in the world (Ebbeling et al. 2002): The world health organization (WHO) states that "Childhood obesity is one of the most serious public health challenges of the twenty-first century. The problem is global and is steadily affecting many low- and middle-income countries, particularly in urban settings. The prevalence has increased at an alarming rate. "Globally, in 2010 the number of overweight children

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under the age of five is estimated to be over 42 million. Close to 35 million of these are living in developing countries"(WHO 2012).

Additionally, it is also well known that obesity in childhood or adolescence not only continues into adulthood (Whitaker et al. 1997; Must and Strauss 1999) but also translates into a higher risk for myocardial infarction and obesity-associated comorbidities in grown-ups (Freedman et al. 2001, 2007). These facts are of enormous importance for the healthcare costs, now and in the future (Cawley 2010): Within a few decades obesity and obesity-associated hospital discharge diagnoses and costs of hospitalizations tripled among children and adolescents (Ogden et al. 2010; Wang and Dietz 2002; Trasande et al. 2009). "Obesity in children and adolescents represents one of the most frustrating and difficult diseases to treat" (Barlow and Dietz 1998)—this might be even truer in *morbidly* obese adolescents (Reinehr et al. 2013; Siegfried et al. 2006).

"For an increasing number of morbidly obese adolescents, who suffer from the consequences of obesity and have failed organized attempts to lose weight, bariatric surgery may provide the only practicable alternative" (Inge et al. 2004a). Although, every type of surgery includes a potential risk, there are certain situations, when comorbidities and the amount of overweight outweigh the risks of surgery by far, justifying an operation in well-selected morbidly obese adolescents (Ippisch 2008).

Although, there is increasing evidence to support bariatric surgery in the extremely obese adolescent, a general recommendation for a single specific surgical procedure for all candidates cannot be made at the moment. Nevertheless, more and more data for the two most commonly performed bariatric procedures, Adjustable Gastric banding (AGB) and Roux-en-Y Gastric Bypass (RYGB), in the adolescents demonstrate safety and efficacy (Michalsky et al. 2012; Treadwell et al. 2008). Beside these well-established operations, Sleeve gastrectomy is rapidly gaining acceptance in adults, and first weight loss reports demonstrate excellent short-term data also in adolescents (Oberbach et al. 2012; Till et al. 2008; Alqahtani et al. 2012a).

12.2 Patient Selection

According to the ASMBS guidelines published in 2012 (Michalsky et al. 2012), adolescents with a BMI above 35 kg/m^2 presenting with major comorbidities (type 2 diabetes, sleep apnea, pseudotumor cerebri, severe NASH) or a BMI above 40 kg/m^2 combined with other comorbidities (e.g., hypertension, insulin resistance, glucose intolerance, substantially impaired quality of life, dyslipidemia) should be considered as candidates for bariatric surgery.

The European guidelines, published in 2007, present similar recommendations for bariatric surgery in adolescents (Fried et al. 2007):

1. BMI >40 kg/m^2 (or >99.5 percentile for respective age) combined with at least one comorbidity

2. The patient has followed at least 6 months of organized weight reducing attempts in a specialized centers
3. The patient shows skeletal and developmental maturity
4. The patient is capable to commit to comprehensive medical and psychological evaluation before and after surgery
5. The patient is willing to participate in a postoperative multidisciplinary treatment program
6. The patient can access surgery in a unit with specialist pediatric support (nursing, anesthesia, psychology, postoperative care)

Special attention should be given to the psychological situation:

Most morbidly obese adolescents are stigmatized by their colleagues and their environment and therefore suffer from a very poor quality of life, comparable to that of cancer patients (Schwimmer et al. 2003).

Overall there is a tendency to intervene earlier (Michalsky et al. 2012), since data suggest that obesity in childhood or adolescence results in shortened life expectancy: For smokers the term "pack years" and for obesity the term "pound years" seem to be appropriate (Baker et al. 2007).

Likely candidates for bariatric surgery should be evaluated in dedicated centers with a multidisciplinary weight management team including:

– High volume bariatric surgeons
– Pediatric specialists
– Dieticians
– Psychiatrist or clinical psychologists
– Physical therapists or activity instructors
– A Coordinator (case manager)

In a review board, the team defines specific treatment recommendations and the appropriateness and timing of the surgical intervention (Inge et al. 2004b).

Special attention should be given to the psychological evaluation not only of the adolescent but also the relation to the parents and the intactness of the family unit and the severity of psychosocial comorbidities: All these factors have significant impact on the overall success of a (surgical) intervention (Whitaker et al. 1997; Dietz and Bellizzi 1999; Epstein et al. 1990; Caniano 2009).

The weight management team should also deal with several ethical issues:

– Is the patient's health (psychic and physical health) compromised by severe obesity (special attention should be given to the presence of depression, necessitating proper treatment)?
– Has the patient failed more conservative options to meet that health need?
– Has the patient decisional capacity?

From these issues it becomes clear that a threshold for bariatric surgery is set at the age of 13–14 years, as at this age decisional capacity matures (Inge et al. 2004a).

Below this age, the adolescents probably will not be able to comprise the consequences of bariatric surgery. Therefore, when approaching this threshold

age of 13–14 years, one should keep in mind the words of Thomas Inge: "The younger the patient, the more compelling and serious (the comorbidity of) obesity should be to prompt surgical intervention"(Inge et al. 2004a).

12.3 Methods

All of the below-mentioned methods are types of bariatric operations that can and should be performed minimally invasive (= laparoscopically) today. This provides the advantage of faster recovery, avoidance of adhesions and incisional hernia, and structural preservation of the integrity of the abdominal wall. In very rare cases a conversion to open surgery may be necessary, e.g., due to adhesions caused by multiple previous abdominal operations. Overall the weight loss outcomes and patient safety in adolescents seem to be at least equal or even better than in adults (Michalsky et al. 2012; Sugerman et al. 2003; Rand and Macgregor 1994; Silberhumer et al. 2011; Lawson et al. 2006).

In bariatric surgery, restrictive operation methods can be distinguished from malabsorptive ones, and some surgical procedures involve both mechanisms inducing weight loss. While restrictive surgery limits the possible amount of oral food uptake by either reducing the volume of the stomach or its diameter, the nutritional absorption remains uncompromised. In contrast, malabsorptive surgery achieves weight loss by the limitation of absorption of nutrients, most commonly performed via bypassing long segments of the small intestine. Some surgical procedures like gastric bypass combine these both weight loss mechanisms.

Excess weight loss (EWL) is the amount of weight lost exceeding a BMI of 25 kg/m^2 in percent. For example, a patient with a height of 1.60 m and a body weight of 64 kg has BMI of 25 kg/m^2. Everything above 64 kg is considered as "excess weight." If someone at 1.60 m weights 124 kg, excess weight encounters an amount of 60 kg. If the total weight decreases to 84 kg postoperatively, he has lost 40 kg of the total of 60 kg excess weight, corresponding to an EWL of 66.6 %.

Weight regain is the opposite of sustained weight loss. Significant weight regain is often defined as a regain in weight of more than 10 kg from the leanest body weight after surgery.

12.3.1 Laparoscopic Adjustable Gastric Banding

Laparoscopic Adjustable Gastric banding (LAGB) is the simplest type of bariatric surgery. It is a purely restrictive procedure, as it only involves the reduction of the functional volume of the stomach limiting food intake without interfering with the normal digestive process.

An inflatable silicone band is placed around the stomach below the cardia, creating a small pouch and a narrow passage into the larger remaining distal part

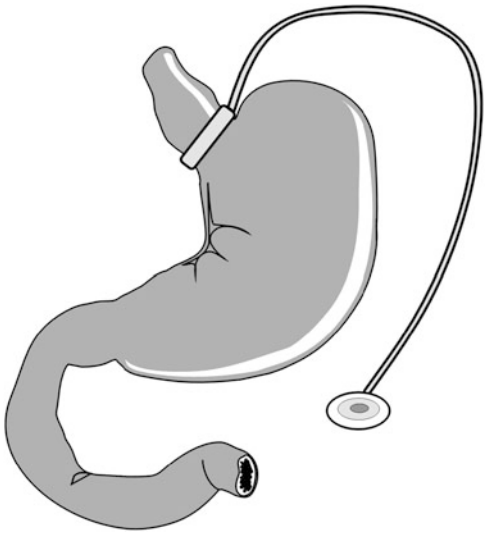

Fig. 12.1 Adjustable gastric band

of the stomach. This small passage ("stoma") delays the emptying of food from the pouch and induces a feeling of satiety (Fig. 12.1). A silicone tube connects the band to a port which is placed subcutaneously (Fig. 12.2) and can be punctured to adjust (widen or loosen) the inner diameter of the band (Fig. 12.3).

Although short-term and mid-term results in adults and adolescents seemed to be promising in the first run (Silberhumer et al. 2006, 2011; Nadler et al. 2008), long-term results show a high reoperation rate and considerable weight regain in a significant number of patients (Lanthaler et al. 2009, 2010; Himpens et al. 2011; Widhalm et al. 2011). Other long-term problems include esophageal dilatation, band migration, changes of eating habits towards increased intake of simple carbohydrates, sweets, and soft drinks, and recurrent vomiting due to poor eating habits or overinflation of the band. In the last 2 years, a worldwide strong decrease in the use of gastric bands in Europe and the USA could be observed (unpublished data, presented by Henry Buchwald at IFSO 2012 New Delhi). Nevertheless, some centers still report excellent long-term results after gastric banding (O'Brien et al. 2013).

A mean EWL of 30–50 % can be expected in the long-term run following gastric banding. The main advantages of the gastric band are that the anatomy of the gastrointestinal tract remains untouched and that the band can be removed laparoscopically. The absence of any gastrointestinal anastomosis accounts for the lowest perioperative morbidity and mortality rate of any bariatric surgery procedure. Furthermore, the untouched calcium metabolism accounts for a higher peak bone mass—which is shaped in the youth and important for osteoporosis in adulthood—than in malabsorptive methods (Weaver 2008).

The main disadvantage of gastric banding is its limited weight loss success. While the short- and mid-term data was promising, the long-term effects on

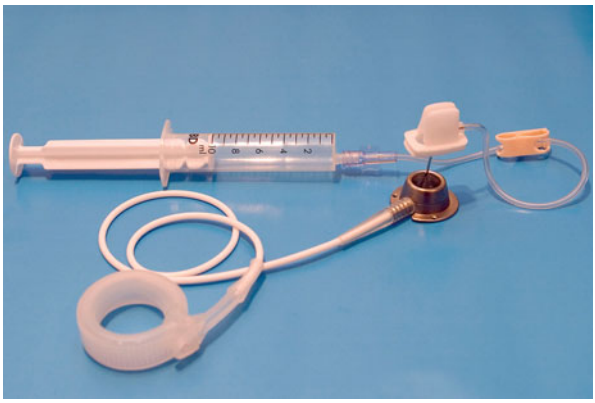

Fig. 12.2 Filling of the band

Fig. 12.3 Filling of the band

maintaining sustained weight loss were disillusioning (Widhalm et al. 2011). Additionally, this type of surgery is contraindicated in eating disorders like binge eaters and patients with Prader–Willi syndrome.

Between 2000 and 2012 a total of 19 adolescents presenting with a mean BMI of 47.9 kg/m^2 $\pm$ 3.5 kg/m^2 (range 41.0–54.3 kg/m^2) underwent gastric banding at our department without any postoperative complications. After promising initial weight loss success (Silberhumer et al. 2006) in the longer follow-up, more and more patients present with significant weight regain. Three adolescents already underwent conversion to gastric bypass, while another two patients actually want the band to be removed.

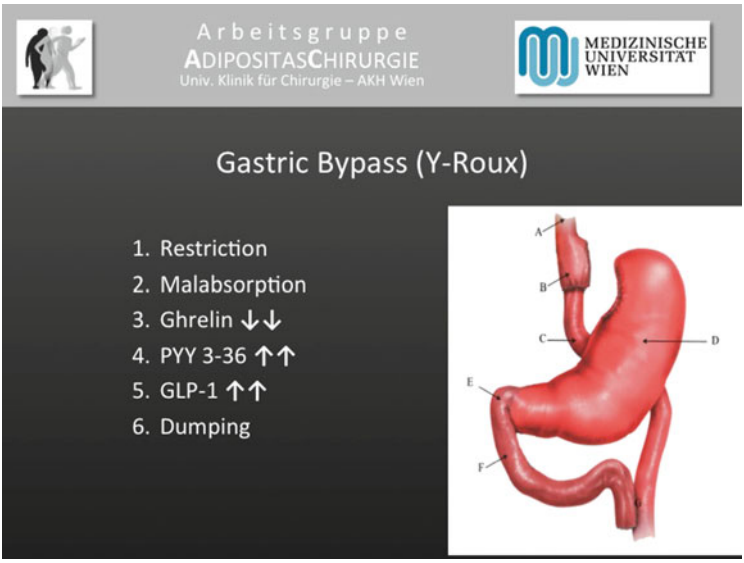

Fig. 12.4 Gastric bypass: mechanism of action. A: Esphagus; B: Gastric pouch; C: Alimentary limb; D: Gastric remnant; E: Duodenum; F: Biliopancreatic limb; G: Jejuno-Jejunostomy

12.3.2 Gastric Bypass

Gastric bypass, the most commonly performed bariatric procedure in high volume centers all over the world, is based on a combination of strong restrictive and mild malabsorptive effects. Furthermore, gastric bypass results in an increased secretion of incretins (Glucagon Like Peptide 1: GLP-1) and the "ileal brake hormone" PYY 3-36. Other possible mechanisms of action include alterations in the Ghrelin secretion and the occurrence of dumping (Fig 12.4).

Though, it is not as simple to perform as gastric banding, excellent long-term data are available. The RYGB involves the creation of a small gastric pouch of only 15–20 mL (restrictive part). Thereafter, the small intestine will be divided and the distal segment anastomosed with the gastric pouch ("alimentary Limb"). Finally, in order to provide bile and digestive enzymes to the nutritional pathway, a second anastomosis between proximal small bowel and the "alimentary limb" is necessary. The typical length of the alimentary limb in RYGB varies between 100 and 150 cm (standard RYGB, long limb RYGB). The distance of the second anastomosis (the length where actual nutritional absorption can take place) can be chosen to fit the individual patient's needs (malabsorptive part, Fig. 12.4). An EWL of 60 % at 12–18 months postoperatively can be expected. Furthermore, the maximum EWL depends on the initial weight: the higher the preoperative BMI, the higher the BMI remains afterwards (Inge et al. 2010). This is the reason why surgery should not be delayed even in adolescents, especially when comorbidities are given.

Remission rates of type 2 diabetes mellitus in adults of up to 80 %—defined by a normalization of all clinical and laboratory parameters in the absence of further required drug treatment—were reported following gastric bypass (Buchwald et al. 2009). In adolescents these results even may be better due to an earlier intervention in the course of the disease (Inge et al. 2009). These effects cannot be explained by weight loss alone, since they take place as early as a few days after surgery in the absence of significant weight loss (Pories et al. 1995). Several theories focusing on changes in gastrointestinal hormones (GLP-1, GIP, PYY3-36, Ghrelin. . .) are being evaluated (Dixon et al. 2012). Bypassing the pylorus and duodenum leads to an earlier contact of nutrients with neuroendocrine cells in the small intestine resulting in an increased secretion of gastrointestinal hormones and therefore optimizing glucose metabolism (Laferrere 2011).

The advantages of gastric bypass surgery consist in the excellent long-term results of sustained weight loss and the remission of comorbidities, which account for the majority of morbidity and mortality of obesity.

The disadvantage of gastric bypass surgery is found in a higher perioperative complication rate when compared to gastric banding, due to the technically more demanding operation (i.e., requirement of two anastomoses). Another disadvantage is the requirement of lifelong follow-up due to development of vitamin and micronutrients deficiencies caused by malabsorption. This, in conjunction with compliance especially in adolescents should be considered carefully (Rand and Macgregor 1994). Additionally, an impaired peak bone mass due to malabsorption has to be expected. Routine supplementation with Calcium and Vitamin D is needed to prevent reactive hyperparathyroidism, loss of bone mass, or osteoporosis in the long-term run: A phenomena known from adults (Coates et al. 2004; Mahdy et al. 2008; von Mach et al. 2004) and adolescents (Kaulfers et al. 2011) after RYGB.

In some patients, even after gastric bypass, weight regain can be observed: Either due to pouch dilatation, dilatation of the gastrojejunostomy, or significant eating of simple carbohydrates.

Rapid pouch emptying might also be the main cause for the so-called late dumping syndrome (or hyperinsulinemic hypoglycemia): 1–3 h after a meal uptake significant hypoglycemia can occur due to an oversecretion of GLP-1. Dietary counseling with avoidance of simple carbohydrates and a diet based on food with a low glycemic index should be done. Further conservative treatment options include Acarbose, Diazoxide, and Sandostatin; but the adherence to these medications is low in the long term due to side effects (Cui et al. 2011; Ceppa et al. 2012; Myint et al. 2012; Valderas et al. 2012).

Surgical treatment for dumping aims on delaying the emptying of the gastric pouch: A procedure that is successful in the majority of patients suffering from hyperinsulinemic hypoglycemia (Z'Graggen et al. 2008).

At total of 48 adolescents with a mean BMI of 48.3 kg/m^2 ± 10.3 kg/m^2 (range 40.9–73.2 kg/m^2) underwent gastric bypass surgery at our department from 2006 to 2012, including two patients with former sleeve gastrectomy and two patients after gastric banding. In 34 patients, a RYGB was performed while 14 patients

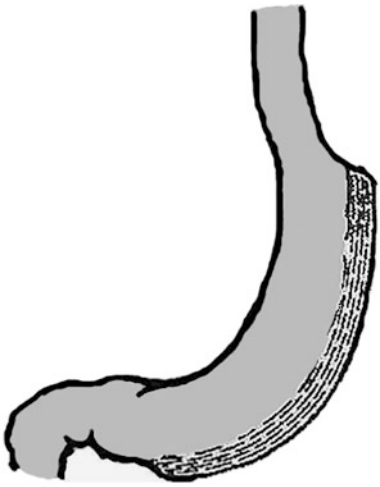

Fig. 12.5 Sleeve gastrectomy

underwent an omega loop bypass, a modified mini-bypass reduced to one single anastomosis between the gastric pouch and a jejunal loop. A total of two patients underwent early postoperative re-intervention after RYGB for leakage at the gastroenterostomy, treated by stent placement. Some weight regain occurs regularly after gastric bypass. In two patients placement of a band around the gastric pouch was performed to counteract weight regain of more than 10 kg at 4 and 6 years following RYGB. In both patients, significant weight loss was re-induced.

12.3.3 Sleeve Gastrectomy

Sleeve gastrectomy, originally developed as a two-stage approach for super-obese patients, has evolved to a definitive single step procedure during the last decade. Initially, sleeve gastrectomy was intended as a first and simpler procedure in super-obese patients to initiate weight loss. In a later planned second step, biliopancreatic diversion with duodenal switch or gastric bypass was completed to achieve further weight loss. Today's perception of sleeve gastrectomy as bariatric procedure has changed to a definitive and one-step solution for obesity. It is a strictly restrictive surgery involving the creation of a narrow gastric tube and resecting the remainder of the stomach (Fig. 12.5). The intestinal continuity is left untouched. This procedure seems not to be appropriate for sweet eater. Weight loss success resulting in an EWL of 50 % can be expected in adults. In adolescents data remains scarce. In a recent study a short-term weight loss of above 90 % was reported (Boza et al. 2012).

Sleeve gastrectomy also results in a sustained reduction of the secretion of Ghrelin, which is a powerful orexigenic hormone (Kojima et al. 1999; Ariyasu et al. 2001). Ghrelin is secreted predominantly in the gastric fundus, which is completely resected in this procedure (Bohdjalian et al. 2010; Langer et al. 2005).

Bohdjalian et al. showed significantly reduced Ghrelin levels at 5 years after sleeve gastrectomy (Bohdjalian et al. 2010).

The main disadvantage of this method is its irreversibility, which is of relevance in adolescents. While gastric banding and gastric bypass can be reversed to preoperative anatomy, this cannot be done after sleeve gastrectomy due to definitive resection of the excess stomach. Additionally, up to 40 % of patients suffer from reflux postoperatively. Furthermore, weight regain remains a problem at least in adults. Finally, as mentioned above, data in adolescents (Nadler et al. 2012) and long-term data in adults remain scarce (Oberbach et al. 2012; Till et al. 2008; Alqahtani et al. 2012a, b; Boza et al. 2012; Bohdjalian et al. 2010; Rosenthal et al. 2012).

We performed sleeve gastrectomy in a total of six adolescents presenting with a mean BMI of 48.5 kg/m^2 ± 10.0 kg/m^2 (range 40.0–71.3 kg/m^2), including one patient with Prader–Willi syndrome. After promising initial weight loss, two patients underwent conversion to gastric bypass due to weight regain.

12.3.4 Biliopancreatic Diversion

Biliopancreatic diversion (BPD) strictly acts as a malabsorptive operation (Scopinaro et al. 1998) involving the creation of a gastric pouch of 200–500 mL, dividing the small intestine bringing the distal loop up for anastomosis with the gastric pouch (alimentary limb 200 cm) and anastomosing the remaining biliopancreatic limb at 50 cm orally of the ileocoecal valve (common limb 50 cm) (Fig. 12.6). Nutrient absorption happens at 250 cm while fat absorption is limited to the last 50 cm of the distal ileum; therefore, fat uptake is vastly reduced. Furthermore, BPD is achieving the highest sustained weight loss of all procedures (approximately 75 %). Additionally, it is especially appropriate for diseases with uncontrollable food intake like binge eating disorders or in patients with Prader–Willi syndrome. Furthermore, BPD has also the highest potential for comorbidity (diabetes, hypertension, and obstructive sleep apnea) resolution (Scopinaro et al. 2005).

The main disadvantage is the malnutrition that can turn out to be unmanageable even with maximum supplementation of protein, vitamins, and micronutrients. Reactive hyperparathyroidism can lead to a reduced peak bone mass (Kelly et al. 2009) or even demineralization of the bone with consecutive hyperparathyroidism. In a large series of adolescent patients, 20 % of patients underwent reoperation, 11 out of 68 developed protein malnutrition, and 7 out of 68 patients had to be reversed to normal preoperative anatomy (Papadia et al. 2007).

In three adolescents with Prader–Willi syndrome, BPD was performed at our department, achieving mid-term weight loss success in all three patients.

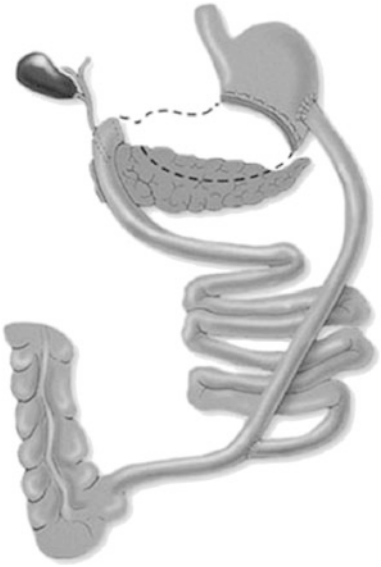

Fig. 12.6 Biliopancreatic diversion

12.4 Complications After Bariatric Procedures

Nonspecific complications after laparoscopic surgery include (immediate) postoperative bleeding, infection, and trocar hernia. Furthermore, each type of bariatric procedure encounters its specific risk profile for surgical and nutritional complications beside possible weight loss failure.

Specific complications after gastric banding include slipping of distal parts of the stomach through the band, pouch dilation, and esophageal dilatation in the long-term run. Furthermore, migration of the band through the gastric wall can occur, mostly in patients with the band adjusted too tight. All these complications contribute to the high-reoperation rate in the longer follow-up following gastric banding (Lanthaler et al. 2009, 2010; Himpens et al. 2011). In case of band failure, conversion to gastric bypass is recommended to re-induce weight loss. Prolonged vomiting can lead to a depletion of thiamine stores within 6–8 weeks: After infusion of glucose, patients can present with psychiatric/neurological symptoms (Beri-Beri disease, Wernicke Encephalopathy). Immediate i.v. infusion or i.m. injection of 50–100 mg of thiamine is recommended.

Following gastric bypass, the most feared complication is leakage at the level of the gastro-jejunal anastomosis, requiring careful management consisting in placement of a self-expanding esophageal stent, drainage, and early reoperation when indicated clinically. Anastomotic stenosis can be usually treated by endoscopic dilatation. In about 3–10 % internal hernia can occur: Vomiting after gastric bypass especially in combination with sudden abdominal pain should always alert physicians to think of the presence of an internal hernia: Immediate re-laparoscopy and closure of the mesenteric gap and/or the so-called Petersen-Space using a running,

non-absorbable suture (the space between the mesentery of the alimentary limb and the mesocolon) are mandatory. Other possible complications are protein-calorie malnutrition and, besides iron and calcium, also micronutrient deficiencies which require lifelong follow-up and compliance with micronutrient supplementation (Rand and Macgregor 1994).

The most challenging complication following sleeve gastrectomy is leakage at the proximal staple line near the angle of His. Like in gastric bypass, leakage management consists in placement of a self-expanding stent, drainage, and early reoperation. Some patients presenting with unmanageable severe gastro-esophageal reflux require conversion to gastric bypass.

In BPD, severe protein malnutrition is the major problem, especially in the adolescent period. Furthermore, steatorrhoe might be a sequel of excessive fat uptake, leading to stinky fatty stools. Therefore, at this age, this operation should be limited for patients with Prader–Willi syndrome.

12.5 Nutritional Risks

Nonadherence or noncompliance of adolescents to take the prescribed supplementation and to participate in the follow up program are well-known phenomena and should be given special attention in the evaluation of morbidly obese adolescents for an operation (Rand and Macgregor 1994; Alvarez-Leite 2004).

Rand and Macgregor (1994) showed in 34 adolescents 6 years postoperatively an excellent result in terms of weight loss, self-esteem, and social integration and development of adolescents. Nevertheless, only 4 out of 34 took the prescribed supplementation and furthermore poor compliance to exercise was found.

Although after gastric banding the need for supplementation is less pronounced, there are also substantial risks for thiamin deficiency in case of prolonged vomiting.

For sleeve gastrectomy one should keep in mind that Vitamin B12 deficiency can occur. Gastric Bypass patients should be monitored for low levels of iron (ferritin/transferrin), Vitamin D, and Vitamin B12 and reactive hyperparathyroidism (reflecting a negative calcium metabolism). This is of special importance because adolescents have not reached their peak bone mass yet (Weaver 2008; Harkness and Bonny 2005).

12.6 Summary

Gastric bypass surgery is considered safe and effective in extremely obese adolescents when stringent long-term follow-up is provided: Excellent long-term weight loss is observed after gastric bypass surgery.

Sleeve gastrectomy should be carefully evaluated in prospective studies. The irreversibility of the operation, the potential reflux, and the high leakage rate of

some series, observed in adults, should be taken into consideration (Pequignot et al. 2012).

BPD should not be recommended for weight loss surgery in adolescents due to the high risk of malnutrition limiting this procedure only for Prader–Willi syndrome patients.

The decision-making process should always be conducted by an interdisciplinary team at an appropriate center for bariatric surgery in adolescents. Furthermore, comorbidities such as diabetes, hypertension, sleep apnea, and hyperlipidemia should be considered carefully in this process.

Postponing the operation into adulthood can likely result in a reduced life span or adverse events before a potential curative procedure can take place: "treatment delayed may be treatment denied" (Garcia 2005).

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Chapter 13
Situation in Sweden

Carl-Erik Flodmark

13.1 The Prevalence of Obesity in Sweden

13.1.1 Levelling-off

Paediatric obesity has increased substantially (fourfold increase) in Sweden as well as in other countries from 1984 to 2004 in 10 year olds (Marild et al. 2004). Moreover, several publications have showed a levelling-off of the increase in obesity prevalence in Sweden as well as in other countries for both children (from 1999 to 2003 in 10 year olds) and adults (Sundblom et al. 2008; Sundquist et al. 2010; Zellner et al. 2004). However, the situation in Malmö has changed recently (Haak 2010). See Table 13.1. This might indicate a general change in Sweden or a local change due to population changes. The report is based on approximately 3,000 children 10 years of age for each year but the drop out rate is not given. Usually, the coverage is above 95 % in the measurements at school of weight and height. In Malmö 39 % in 2010 are born abroad or have both parents born abroad. This indicates the population has a mixed background and that the observation might be generalisable.

13.2 Prevention in Sweden

Sweden has a long tradition of preventive work, both in school health care and in child health care. Usually, 95–98 % of all children attend child health care, and school education is an obligation by law. This indicates that school health care

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Table 13.1 Proportion overweight in % (20.00–23.99) or obese (≥24) in 10 year olds school year 4)

Year	Girls overweight	Girls obesity	Boys overweight	Boys obesity
2003/2004	19	6	17	6
2007/2008	17	6	19	6
2008/2009	19	7	17	7
2009/2010	20	8	19	9

reach the majority of the population. Height and weight should be measured regularly at school.

Thus, preventive actions have been studied in Sweden indicating that this is a useful strategy. Sweden has participated in the IDEFICS study (Ahrens et al. 2011; De Henauw et al. 2011). Furthermore, specific interventions have been designed (Marcus et al. 2009). The national Swedish Health Technology Assessment body has previously evaluated preventive actions in health care (Flodmark et al. 2006).

13.3 Quality Assessment in Sweden

A Childhood Obesity Database has been set up in Sweden 2005 (Marcus 2011). A national steering committee is responsible for the register. In 2010 5,305 patients have been included reporting 15,656 visits. There were 720 new patients. The age was 10.4 ± 3.6 SD with a BMI SDS 4.85 ± 1.8 (Rolland-Cachera) or BMI SDS 3.2 ± 0.74 (Karlberg). Most of the paediatric units in Sweden are participating (21/35). No follow-up data has yet been published from the register.

There is no other system that might influence the choice of treatment or preventive actions. Almost all health care is tax financed and organised into 21 regional areas with locally elected politicians that directly run and control hospitals, health care centres, school health care etc. On an outpatient basis a small private sector is now emerging as a GP system but no specialisation into obesity has yet been occurring. Also some schools are private but the health care system is then usually not supported more than in the schools owned by the county. There is usually no incentive to improve quality through quality indicators influencing the budget. Huge resources are put into health care providers financed and controlled by the political system but their development of new methods has not been supported in such an extent that a national preventive or treatment plan or actions have been developed. Thus, there is a great need of focussing on the methods used in health care against obesity.

13.4 Obesity: A Disease Put into Perspective

How do we discover the cause of a disease? This is a major scientific problem in medicine. Usually, we are trying to find THE cause of a disease. However, a problem arises when a disease is caused by different factors. Suppose, obesity is caused by five different genes and also suppose these genes to be of equally importance. In trying to identify the strongest factor chance will give us different answers in each study. There will arise a debate which factor is the strongest. The more equal the factors are, the more difficult it will be to solve the controversy.

However, we can accomplish a new understanding if we accept that there are several different factors (genetic and social) causing obesity.

A simple way of classifying obesity would be into early and late onset obesity. Early onset obesity, predominantly inherited, gives a large body size with a moderate increase in cardiovascular health risks as opposed to late onset obesity, predominantly lifestyle dependent, giving visceral adiposity with a greater increase in cardiovascular health risks. Of course life style is also important in early onset obesity, as is the inheritance in late onset obesity.

However, due to the multifactorial causes of obesity, it is necessary to treat it in a combined approach with many different components in the treatment programmes, i.e. combining advice about exercise, diets and training in social skills or even drug treatment or surgery in the most severe cases.

13.5 Why Do We Need New Treatments?

Many different treatments of obesity have been investigated, including diet, exercise, surgery and medication. None have been found to be effective enough as the sole treatment.

It is now also clear that treatment needs to be affirmative and long lasting. Single physical treatments are insufficient because of the accompanying psychological factors, and brief treatments fail to take account of the lifelong genetic influence.

The necessity of a chronic treatment is now more widely recognised. This is due to the increasing knowledge in genetics where many obese patients have an inherited susceptibility of developing obesity. Thus, they need treatment all life and not merely a short period of training in a good exercise or diet programme. After such a period the problem of obesity used to be thought of as gone and the individual could go back to earlier but somewhat improved lifestyle without risking the development of obesity. If they gained weight it was thought that their lifestyle was more unhealthy than the lifestyle of normal-weight persons. Now, the genetic discoveries give room for another interpretation. Furthermore, the concept of programming our genes early in life might explain how genes and environment interact in a more complicated way.

If you have inherited the disease obesity, it is not enough to live as normal weight people do regarding exercise and diet—you have to live more than perfect. Below, we will describe what strategies to choose from. Of course, if you have no genetic susceptibility for obesity, it is much easier to reduce weight. Just live like other people of normal weight do! However, if you have the genes or genes that have been programmed to increase your weight your lifestyle needs special care!

13.6 Behavioural and Cognitive Therapies

Behavioural therapy has been used in obesity management since first described (Stuart 1967). The programme was based on the belief that obesity is a "learned disease", possible to cure by "re-learning". However, successful long-term results have not been achieved in adults (Brownell and Wadden 1991). Nonetheless, a 10-year follow-up without control group did show lasting results when booster sessions were given for a period of 4 years. This indicates the difficulties of preserving good results and the need for long-term treatment (Björvell and Rössner 1992).

Behavioural therapy of obesity is based on the concept of bad eating habits in which an insufficient control of stimulus or rewarding behaviour results in increased food intake. These habits can be broken down into small sequences, e.g. the frequency of chewing of meals, etc. The parents are regarded as a reinforcement of the children's eating habits. For example, a deposit of money may be paid back to the patient during weight reduction (Epstein et al. 1980).

In 1983, Brownell and co-workers evaluated a programme consisted of behaviour modification, social support, nutrition and exercise (Brownell et al. 1983). They noted that groups, in which obese children and their mothers met the group therapist separately, gave better results than those in which only the children were seen or the children were seen together with their mothers.

Others also studied the effects of parent interaction, using three groups (Epstein et al. 1990). The first group consisted of child and parent where parent and child behaviour change and weight loss were reinforced by behavioural techniques, the second group consisted of children only and child behaviour change and weight loss were reinforced, and in the non-specific control group families were reinforced for attendance. The best result was achieved in the parent and child group.

Furthermore, cognitive therapy has been used in the treatment of obesity usually combined with behavioural therapy. This combination is based on the assumption that, through practice and reward, changes in key areas of children's cognitive processing will result in behavioural changes. However, the causal connections between the attempt to influence the child's cognition and the observed behaviour changes have not been studied with stringent research designs (Kendall and Lochman 1994).

There have been few studies evaluating cognitive with behavioural therapy. In one such study 27 children aged 7–13 years were randomised to either cognitive

therapy or behavioural therapy. No differences were found after 3- and 6-months follow-up, and the therapies were equally effective (Duffy and Spence 1993). The follow-up period was short, however.

In another study behavioural treatment was combined with either cognitive therapy or nutrition education (Kalodner and DeLucia 1991). The different treatments induced different ways of controlling the weight; for instance in the cognitive group the weight-related cognitions were more adaptive than in the other groups. However, the analysis showed that there were significant differences regarding the obesity status across time but not between the different treatments. Finally, another study with 3-months follow-up also showed that the addition of cognitive therapy to a behavioural programme gave no further improvement than behavioural therapy itself (DeLucia and Kalodner 1990).

Finally, Caroline Braet has showed that cognitive therapy is effective in treating childhood obesity (Braet et al. 1997). The treatment was combined with family talks although regular family therapy was not given. Although emerging from different therapeutic backgrounds, this programme has many similarities with the programme based on family therapy (Flodmark et al. 1993). These two studies show that a combined programme is effective using a careful selection of different approaches.

13.7 Group Therapy

Many different types of therapy can be utilised within the context of a group, and there have been some studies of this approach. For example a peer group behaviour modification programme of adolescents gave better results than previous individual contacts (Zakus et al. 1979). However, the development of group cohesion was tenuous and temporary. Girls who were functioning more independently appeared to do better in weight loss. The study was not randomised and the patient group was small. In another study individual dietetic counselling, group dietetic counselling and group dietetic counselling with behaviour modification were compared (Long et al. 1983). The first and last treatments were equally effective at 1-year follow-up and better than group dietetic counselling alone. The general impression has been that group therapy has no decisive advantages upon individual therapy (Aimez 1976). Exceptions may include those groups, which we carefully select so that they are strongly homogeneous regarding e.g., gender, age and social background.

In preschool children it is probably easier to get the children's acceptance of a group formed by adults. Later on the children need to create their own groups. Probably, activities in groups might be more successful in preschool children than later on.

However, if you combine the meeting in a group with a more specific method treatment might be effective for some groups. A Family Weight School treatment model was developed within the framework of SOFT (see below), setting up a 1-year programme consisting of four group meetings (Nowicka et al. 2008). Up to

12 families participated at each 4-h meeting. A total of 65 out of 72 adolescents completed the programme. The participation in the Family Weight School resulted in a significant decrease in degree of obesity in adolescents with BMI z-scores below 3.5 [adult equivalent approximately BMI 40 (Daley et al. 2006)], but not in adolescents with BMI z-scores above 3.5 compared with a waiting list control group. Thus, the Family Weight School has been shown to be effective in treating adolescents with severe obesity but not for those with morbid obesity.

This shows that it is not sufficient to set up a group treatment programme without adding a specific method. The encounter of a group could be as varied and based on several different methods as an individual meeting would be. Thus, the classification in Medline using group therapy as a specific Mesh term is not clear enough. This is also so for the Mesh term family therapy where the meeting of the family is not the only criteria that is important in defining the type of therapy.

The Mesh term behavioural therapy is not focusing on whether you see an individual, a family or a group. Thus, group therapy and family therapy should be given new definitions. Group therapy should be classified according to the psychological technique used. The most common form of family therapy should be given the name of systemic therapy (see below).

13.8 School-Based Treatments and Prevention

It is difficult to give prevention at school without needing to give treatment to the most severe cases. Thus, a good prevention programme needs to be backed up by a good treatment programme.

Behavioural therapy has also been used in a school setting (Brownell and Kaye 1982). The programme consisted of behaviour modification, nutrition education and physical activity. Parents and school personnel were involved. Sixty (95 %) of the 63 children (5–12 years) in the 10-week programme lost weight, compared to only 3 (21 %) of the 14 control children. The programme children showed a mean decrease of 15.4 % in their percentage overweight and lost an average of 4.4 kg.

Providing treatment in a wider context at school and furthermore perhaps not only promoting a good lifestyle not only to obese children but also to ALL children may be a fruitful approach. However, long-term follow-up is difficult in such studies, with so many individuals being treated and so many variables to be controlled for. School-based treatments have been reviewed but no single programme was significantly better than the others were thus no recommendations could be made (Ward and Bar-Or 1986). Most of the programmes are not directed to obese children but instead to groups of all children.

School-based programmes often get the aim of acting as a prevention strategy. The Swedish Council on Technology Assessment in Health Care (SBU) did an analysis of prevention studies in childhood obesity (Flodmark et al. 2006). The conclusion was that prevention probably is efficient although there is no overall

identifiable method that could be recommended. This shows the importance of focusing more on the methodological issues.

A successful programme in Sweden has been developed (Marcus et al. 2009). This study also investigated the influence of a preventing programme on obesity regarding eating disorders. Ten schools were selected in Stockholm county area and randomised to intervention ($n = 5$) and control ($n = 5$) schools. Low-fat dairy products and whole-grain bread were promoted, and all sweets and sweetened drinks were eliminated in intervention schools. Physical activity was aimed to increase by 30 min per day during school time and sedentary behaviour restricted during after school care time. Physical activity was measured by accelerometry. Eating habits at home were assessed by parental report. Eating disorders were evaluated by self-report. The prevalence of overweight and obesity decreased by 3.2 % (from 20.3 to 17.1) in intervention schools compared with an increase of 2.8 % (from 16.1 to 18.9) in control schools ($P < 0.05$). The results showed no difference between intervention and controls, after cluster adjustment, in the longitudinal analysis of BMIsds changes. However, a larger proportion of the children who were initially overweight reached normal weight in the intervention group (14 %) compared with the control group (7.5 %), $P = 0.017$. Physical activity did not differ between intervention and control schools after cluster adjustment. Eating habits at home were found to be healthier among families with children in intervention schools at the end of the intervention. There was no difference between children in intervention and control schools in self-reported eating disorders.

13.8.1 Early Treatment

Early treatment, i.e. started before the major peak incidence of childhood obesity at the age of 10, has shown better results for preschool children than older children (Davis and Christoffel 1994). This type of treatment is in one way similar to school-based treatment as it is common to use groups of children but differs in being directed to *obese* children (see above). Furthermore, treatment of children seems to be more effective than treatment of adults (Epstein et al. 1995). Moreover, 50–75 % of adults in excess of 160 % of ideal body weight were obese as children (Dietz 1983). Thus, early treatment would prevent the most severe cases of obesity in adults.

However, no study has been performed comparing early to late start of treatment. An indication that it could be useful could be found in the Boris register where early treatment seems to be helpful (Marcus 2011).

13.9 Family Therapy

The family is regarded as basic to the child's psychological development and a major factor influencing the child's quality of life. Family therapy has been used for children with behavioural and/or emotional disturbances and for children with chronic diseases.

Many studies have been performed and they have been evaluated in several reviews (Gurman and Kniskern 1981; Hazelrigg et al. 1987; Lask 1987; Dare 1992).

These show family therapy to be effective in asthma, diabetes, anorexia nervosa, bereavement and adult schizophrenia. It has also been possible to develop family-based diagnostic tests for those families where a child is showing different symptoms (Hansson 1989).

Psycho-educational family therapy has been used in schizophrenia. Orhagen and co-workers have studied whether the educational or the therapeutic part of the programme was most effective and showed that both are needed (Orhagen 1992). Another Swedish study has shown family therapy to be a cost-effective treatment for childhood asthma (Gustafsson 1987).

It has also been suggested that family therapy might be helpful for treating obesity (Ganley 1986).

Epstein has shown in several studies the importance of the child's interaction with its parents (Epstein et al. 1980, 1990).

The author and co-workers have shown that the use of family therapy in treating obese children in a population screened at school prevents the progression of obesity in older teenagers if treatment is started at the age of 10 (Flodmark et al. 1993). The families were selected from a population-based sample and three groups were compared. The first group received conventional treatment, i.e. regular visits to a physician and a dietician; the second group underwent six sessions of family therapy. In both groups the duration of treatment was 14–18 months. The third group received no treatment.

At follow-up 1 year after the end of treatment, the body mass index was significantly lower in the family therapy group than in the untreated control group. Furthermore, physical fitness was significantly higher in the family therapy group than in the conventionally treated group, and the fat mass (measured by skinfold thickness) was significantly lower. There was no difference between the family therapy group and the conventional treated group regarding body mass index. This might be due to the better physical fitness in combination with the reduced fat mass leading to a higher muscular mass thus increasing body mass index.

13.10 Systemic Family Medicine

Family therapy has been tried as treatment in several chronic diseases. However, the techniques are not adapted to the disease. It is important not only to know how to give a message but also to give a message that makes a meaning relating to the problems given by the disease. Furthermore, the medical condition, in this case obesity, also needs to be addressed. It is better to give the medical treatment as an integrated part of the overall treatment.

Systemic family medicine is a field of medicine that can be defined by an integration of system theory, family therapy, general practice and modern clinical medicine (Flodmark and Ohlsson 2008). In system theory there is a core that says that one cannot understand the wholeness of any phenomenon by examine only its component parts. First, psychiatrists applied system theory in clinical practice in order to treat severe psychiatric cases, and later it also has become a possibility for clinical medicine. In the field of family therapy today systemic family medicine is a useful bio-psychosocial model which gives the doctors and the team a creative complement to the regular medical/biological model. The traditional paradigms of linear causality is here replaced with a circular model where different factors interact and are connected to each other. Illnesses are in this perspective a part of a pattern. Families and networks are often active in a helping process. The therapist is also a part in this ongoing dialogs of communications.

During the decades there have been an increased number of studies concerning the family and the families' influence on chronic illness (Gustafsson et al. 1986, 1987; Lask and Matthew 1979). In most of these studies there is a family dysfunction that is associated with poor coping, low adherence and adverse health outcomes (Larivaara 2008; Larivaara et al. 1994, 2004).

The bodies of research demonstrate that families and their network influenced most of health-related behaviour and bring forward the notion about the limitations to meet the patient alone.

There are several different ways of giving family therapy. However, the basic ideas are the same. First, the ambition to change and develop the family structure, based on the needs of the child and the other family members, is important. Second, the family hierarchy, including grandparents, is taken into account. Third, the major way of achieving these goals is to engage the family by gathering them together to discuss the problems or solutions. Finally, the family life cycle is also important, as needs differ as the family evolves. For instance, an additional child requires a changed family structure in which every member has to adapt and yet still retain his or her own individuality.

13.10.1 Solution-Based Brief Therapy

The solution-based brief therapy is originally emanated from the field of family therapy. The family therapy has its origin in the schools of interactional, relational and systemic theory. From the 1950s the family therapy began to find its roots in the current research about human communication (Bateson 1955, 1956, 1972; Bateson and Jackson 1964) and from that point several kinds of schools have developed. During the 1980s Steve de Shazer (de Shazer 1982, 1985, 1988, 1991) introduced a kind of therapeutical interaction named solution-based brief therapy. This was an unusual therapy that became famous for its originality and for its simplicity; at least on the surface.

Steve de Shazer was inspired and influenced by post-structuralist philosophers such as Wittgenstein and Derrida who were among the creators of the perspectives of constructivism (Derrida 1978, 1981; Wittgenstein 1958, 1975). This describes how you in your inner world, and in dialog with significant others, construct an image of the world you are living in. Our relation to language is also like a barrier which can be passed by communication to other people. As a human being we are using language but the language is also using us. Together this became a map or a construct that is guiding you in life. The construct is continuously changing or maybe it is not.

In the therapeutic interaction the therapist begins a kind of language game "the term means to bring into prominence the fact that the speaking of language is a part of an activity, or a form of life." (Wittgenstein 1958). The language game is in this context a complete system of human communication. The language game is a way to describe that the communication between the therapist and the client has attributes similar as well to any other language systems.

13.11 SOFT

Standardised Obesity Family Therapy (SOFT®) is a use of family therapy in a somatic context treating obesity, as is systemic family medicine mentioned above. The first study developing this model has been described in detail elsewhere (Flodmark et al. 1993). This is one of the few randomised controlled trials in the treatment of childhood obesity that was performed in our centre after screening a general population of school children aged 10–12. The study has been described under "Family Therapy" above. This method has now been applied at the Childhood Obesity unit, University Hospital in Malmö, serving children and adolescents in southern Sweden.

The method has been further evaluated in the practical setting of this tertiary referral centre (Nowicka et al. 2007b).

13.11.1 SOFT Compared to Other Treatment Models

Although treatment approaches effective in the treatment of childhood and adolescent obesity share many similarities, the models are quite different in their underlying treatment philosophies and implementation strategies (Flodmark 2005). The most distinguishing feature of SOFT is the focus on family interactions as an important source for implementing and maintaining lifestyle changes (Flodmark 1997; Flodmark and Ohlsson 2008). SOFT and also family therapy focus on interactions which are not a part of psychodynamic, behavioural or cognitive behavioural based obesity treatment models. Inclusion of families in treatment of childhood obesity is widely used (Kitzmann and Beech 2006; Nowicka and Flodmark 2008; Young et al. 2007). However, SOFT is the only treatment model for obesity that relies on coherent integration of family systems theory and therapy, developed and evaluated in a medical setting. SOFT integrates systemic (Palazolli et al. 1980) and solution-focused theory and principles (de Shazer 1988) and is an empirically validated family therapy model for children and adolescents with obesity. The goal of SOFT is to provide an appropriate level of medical and psychosocial support to families of children with obesity.

13.11.2 Research on SOFT

Several studies have tested the efficacy of SOFT in child and adolescent groups. In the first study, family therapy was found to be effective in the treatment of 10 to 12-year-old obese children (Flodmark 1993). Neither systemic family medicine nor SOFT was established at that time. A study description has been given under "Family Therapy".

In a second study 54 highly obese children and adolescents were offered family therapy by a multidisciplinary treatment team consisting of a paediatrician, a dietician/sports trainer, a paediatric nurse and a family therapist. This intervention resulted in a significant decrease in the degree of obesity of the child, as well as improvement of self-esteem and family functioning (Nowicka et al. 2007a). These results were obtained with 3.8 sessions. Eighty-one percent of the families participated in the follow-up. The treatment offered in this study is part of routine clinical practice in the Childhood Obesity Unit and will be described under "SOFT in practice".

13.12 The Processes in Therapy

13.12.1 Approaching the Family

The major problem in obesity is to establish adequate motivation for long-term treatment success. The thoughts and beliefs of the subject families will therefore be briefly discussed based mainly on our experiences of the study (Flodmark et al. 1993) and the work within Childhood Obesity Unit using SOFT (Nowicka 2009).

In a family in which obesity is frequent, there is a tendency to accept overweight as a positive identification across generation borders. Also, a parent may fear hurting the child physically or mentally by discussing weight control or changes of diet. The therapist had to approach this question with respect.

Different family members showed variations in how they took advantage of the therapy. However, the child was usually the most interested, and therefore most motivated, in regulating his/her weight. This could be related to increasing problems of the pre-adolescent to find suitable, well-fitting clothes, and also to a desire to look more like other children. Yet few of the obese 10–11 year olds reported any problems regarding bullying by other children. They also reported ordinary relationships with friends.

Even if the child is strongly motivated, he or she is closely dependent on the parent regarding choice of food purchased and served in their home. Usually, the families wanted to maintain their habits and an incongruence arose between this desire and the need of change in the family to help the obese child. In this situation, therapy is a means of helping the family try out other solutions to the problem.

13.12.2 The Strategy in Therapy

The most useful strategy was to recommend small and simple changes rather than more complex ones. The effect of a small change regarding diet or exercise, if allowed to exert its influence for a long time, is much greater than major changes that the family cannot maintain. Indeed, by walking or running 4 km a day (equivalent to 200 kcal in a 40-kg child), the child can lose 1 kg within 35 days, or 5 kg in half a year, even without a reducing diet (Bar-Or 1983). Instead, in order to lose 1 kg of adipose tissue in a short period of time and in an unreasonable way, a 40-kg child may have to run 140 km or play tennis for 26 h. This example is also a metaphor for an efficient change according to Steve de Shazer's model.

The therapist used the structural model (Minuchin) as a frame perspective within which the solution-based model (de Shazer) exerted its influence. Usually, the situations which the families wanted to discuss were those in which the child or parents experienced difficulty in following the prescribed diet or recommended exercise, not the recommendations per se.

During therapy adequate information was essential for success in finding solutions. Usually, the family was asked to discuss different solutions at home before the next session. The beliefs and thoughts of the obese child were essential to the process.

13.12.3 Family Interaction

How do families communicate their essential needs with regard to feelings, cognitive information and appreciation? There are indications that the families are not homogenous when their ways of communicating are taken into account. Ways of relating to the obese child cannot easily be generalised, as families are different.

Some general observations will be made, however.

The consequences of weight reduction may result in worries about the health and well-being of the child. Often the parents talked about this openly especially the fear of developing anorexia nervosa. However, the children had much more courage and a more realistic feeling for an appropriate weight goal.

13.12.4 Practical Approach

The treatment lasted for 4–6 sessions and sometimes even shorter. The clients appreciated this kind of therapy which clearly differs from traditional psychotherapy. There is a strict focus on solutions, not on problems like the vast majority of psychotherapy suggests, e.g. psychodynamic therapy. Furthermore, the attitude contains a total respect for the patient and his/hers values. However, it is necessary to bring up a goal in therapy; otherwise it is not possible to conduct any therapy.

In solution-focused therapy small achievable goals are recommended, as the accomplishment of the first goal may lead to the next. There is also a technique of using scale questions to better visualise how the client approaches a goal. The desired state of change is also a question that brings up a lot of creativity and positive feelings. In order to take small steps, the solution talk becomes realistic and invites to focus on change. “Change is inevitable”, a statement by Bateson that takes advantages of a process that is going on either we noticed it or not. It’s a fact of life on this planet (Bateson 1972).

Starting therapy, a process of about 2 years, is initiated with sessions from 2 to 4 times a year. Each session starts with an evaluation of the present situation and together with medical data ends up with a conclusion in the end of session. The family takes an active part in this process. This conclusion is always supportive and delivered in a positive manner. The underlying message is always: you doing your best—and we know it. It also includes appreciation of valuable achievements by the family and further suggests for homework.

13.12.5 The Outlining of the Interview

To start with questions like "What has been working well since we met last?" is often very useful throughout therapy. Thus, the family is given the opportunity to reflect about the favourable circumstances that they have contributed to. Furthermore, the answers are appreciated by the therapist as a sign of positive care by family members. Not only parents but also the child is given credit for these achievements. Thus, positive sequences are initiated. Later on the family's specific problems may be encountered and detailed solutions may be discussed. Usually, the family is eager to discuss how to further reinforce those aspects of the child that are positive and function well.

The good intentions of the family to maintain results are clarified by discussing what every family member has done in detail and how. This creative process is used as a prophylaxis against future difficulties in maintaining normal weight. How different family members recognise the beginning of a relapse is valuable, as the child can be made aware of the dangerous chain of events that can follow. Usually, one or several members of the family are given a task or a question to think over until next time. The session is finished by the therapist complimenting all the members.

At the beginning of the next session the outcome of the task is checked. Thus, a good cycle of events is created and the child is considered to function better. This may be expanded to other areas of life with the help of parents and siblings. Finally, the initial problem of good eating behaviour is regarded as solved although the family is aware of the risk of a relapse. By now they also have a strategy of how to cope with this by reminding the child of the good cycles.

A supervisor and co-therapist were used in the study in 1993 (Flodmark et al. 1993). Before the compliments were given a short break was taken. Later using SOFT the treatment team included several professionals (paediatrician, nurse, dietian, sports trainer, psychologist) and not always a break was taken (Nowicka et al. 2007a).

The therapy included those questions and solutions that the family was ready to discuss. One major topic was IPs' (identified patients) ideal weight and the family's reactions to the beliefs of the child. Often, both child and family had unrealistic expectations when it came to achievable goals. After information on biological limitations, especially in childhood, most families accepted more realistic goals and time schedules for its achievement. Another topic was how great a chance IP had to achieve his or her goal measured on a visual-analogous scale (VAS; from 0 to 10). All family members were asked to give a value which might differ from time to time. The kind of support needed for IP to achieve this goal was discussed. Different suggestions and solutions were listed and discussed. The VAS were also used to measure available resources and this resulted in many good suggestions to both IP and other members of the family.

It was clear from our observations that the family was eager to solve the problem but they lacked effective solutions.

To summarise, the following items were found to be useful:

- Give the family low intensive non-confrontative contact.
- Identify the resources of the family and acknowledge them.
- Show respect for the family and use non-condemning interventions.
- Involve important individuals.
- Try to identify the whole system and relate it to its context.
- Accept the individual's definition of the problem.
- Rephrase in a positive context.
- Emphasise the positive solutions.
- Start with the small simple solutions. Give appreciation.
- Discuss an appropriate realistic ideal weight.
- Inform about the time needed to achieve the goal in the longer term.
- Controlling overweight is hard work.

13.13 A Case

All the family members were seen as being involved and enthusiastic. They all gave many suggestions on how to help IP. The members asked many questions and were eager to collect information given by the therapist. The father was severely obese and had tried many sorts of treatments. He had an impressive knowledge of nutrition and health care issues although he was not able to use it. The therapist gave him the view that he would know what to do when the time came. He was also given credit for his earlier attempts to lose weight. The mother was also severely obese but more successful in her achievements. She was complimented on this.

IP showed strong positive feelings towards her parents, which were confirmed by the therapist. This involved all the members of the family in her problem. The difficulty was defined as finding a suitable strategy and a way of knowing when the right time had come to apply it. The family should be convinced that a solution was close at hand before trying once more. The other children in the family and their experiences of weight control were thoroughly discussed and their strengths emphasised. One of the older children had normal weight and stated clearly that she had the same difficulties as her little sister up to the age of 15. She did not know how she had succeeded, but this was a turning point for her. The therapist emphasised her own effort in this by complimenting her on for her achievement.

All the family members including IP stated that this was also what was going to happen in her case. The therapist stated that this was a good example of what strong conviction may achieve and that IP should be prepared when the time came.

Suggestions were given to the family members as to how to discuss these matters and they were each of them encouraged to give their personal view to IP to increase her readiness to change.

The therapist also asked IP to mention her ideal weight, so she would be more aware of when her goal was reached. IP was eager to discuss this and the family's

reactions to her ideal weight were observed, giving complements to both IP and the other family members due to their good judgement and patience. They were prepared to wait 2 or 3 years for a change to take place.

During therapy the family started with an intensive programme resulting in a substantial weight reduction. The therapist then asked the family how they would notice a relapse as early as possible. Also a slower rate of increase was recommended (a child is not recommended to lose weight at this age; instead they should gradually approach the normal weight for their height as an increase in height naturally increases the weight). This view was well received by the family and was also compatible with their beliefs mentioned above.

In another case interventive interviewing has been described (Flodmark 2005). This technique is using circular and reflexive questions developed by Karl Tomm (1987a, b, 1988). Below a practical example is given.

13.14 The Questions are the Answers

Below is given some examples of how to use the different types of questions in the treatment of obesity in children and adolescents. You are seeing a 15 years boy with his mother and father. The setting might be a doctor's office or a room especially set up for conversational therapy.

13.14.1 Linear Questions

Dr: How are things going with John's obesity?

Mother: He is trying to eat less but I don't know what he is doing when he comes home from school.

Dr: Do you follow the lists I have given to you, John?

John: I have tried to but I don't know where they are.

Dr: When did you see them last?

John: I don't remember.

Father: He is always trying to escape his responsibilities, says my wife!

Dr: Do you remember anything from my lists, John?

John: No, I don't. Didn't I tell you that one minute ago? I want to go home now.

The linear questions although not intended could lead to a scapegoating process. Here, John is blamed for not being able to follow the diet. This was started by the initial complaint of the mother. The doctor used linear questions without the intent of blaming, but this was counteracted as the mother got the support from the father that really did not know what was going on at home.

13.14.2 Circular Questions

Dr: How are things going with John's obesity.

Mother: He is trying to eat less but I don't know what he is doing when he comes home from school.

Now you know that the mother is worried. Instead, you use circular questions to investigate the problem.

Dr: Who would know that?

Father: He is always trying to escape his responsibilities, says my wife!

Now you know the father also is worried but that he does not know what is happening at home when he is not there.

Dr: Who is most worried for your obesity John, your father or your mother?

John: It is my mother.

Dr: How do you know that?

John: She is always nagging about what I am eating when I get home from school.

Dr: Is there any difference in how your mother or how your father reminds you about what your are eating?

John: Yes, my father reminds me but my mother is nagging all the time.

Dr to mother and father: What can you do to help each other to remind John about his late afternoon snack?

These questions are more neutral but still you need to be careful. Although you use circular questions you might need to give the mother more support.

13.14.3 Strategic Questions

Now let us continue the conversation with something more powerful!

These questions are used by lawyers and journalists and are not recommended in obesity. They could be useful in certain psychiatric conditions but an example is given below. The doctor wants to increase the involvement of the father.

Father answers: I don't know.

Dr to father: Can't you see that you make your wife disappointed in not helping her?

Father: I have too much to do at my work.

Dr to father: How is it possible for you to totally abandon your family?

Father: I am really trying you know.

Dr to father: When do you think your wife will let you choose between your job and your family?

After this you might never see the family again. Of course, these questions might be efficient but they are too powerful. Instead reflexive questions are recommended.

13.14.4 Reflexive Questions

Father answers: I don't know.

Dr to father: If you would guess, what would be possible for you to do?

Father: I might call John at home when I have my coffee brake and remind him about what he is going to eat.

Dr to mother: If this was done regularly do you think this would help John in loosing weight?

Mother: Of course it would. I would be so happy if I didn't have to take all the responsibility for John's eating all the time.

13.15 Conclusions and Summary

The situation in Sweden indicates that obesity might still increase in spite of a well-developed system for prevention and health care both before and after school start.

Our own studies in Malmö show family therapy to be effective in preventing the development of gross obesity during childhood (Flodmark et al. 1993; Nowicka et al. 2007b). Furthermore, behavioural therapy and cognitive behavioural therapy show long-term effects (Bakris and Frohlich 1989; Braet et al. 1997; Epstein et al. 1993).

Many studies in childhood obesity treatment does not focus on the methodological questions. This leaves the outcome to the skills of the treatment team that is not described and cannot be conveyed to another study. Moreover, we have the same problem in most prevention trials.

Thus, this is of major importance that the methodological issues will get more attention.

The reasons for treating childhood obesity is the negative long-term effects on health.

It is not known what is the lowest degree of childhood obesity, expressed in BMI, at which future complications such as cardiovascular disease and diabetes start to be over-represented, when compared with the normal weight population. However, both Mossberg (1989) and Must et al. (1992) have demonstrated that obesity in childhood is associated with major adverse health effects.

Based on adoption studies involving obese adults (Sørensen 1991) have shown how genetic and environmental influences on premature death can be distinguished.

Our studies are good examples of a systemic medical approach integrating psychological methods with medical treatment where the different needs of the individual were taken care of with standard family therapy techniques still gaining a good result. However, the need for urgent action regarding childhood obesity makes further research in this field of knowledge necessary.

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Chapter 14
Experiences from Adolescents at the Viennese Center for Bariatric Surgery

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The Viennese center has performed bariatric surgery in adolescents for as long as 8 years to date of publication with special emphasis on detection and prevention of vitamin and micronutrient deficiencies. As a conclusion to this chapter we want to share our experiences with long-term follow-up after bariatric surgery and the associated secondary complications. The results mentioned below were partially published in Pediatric Obesity in 2011 (Widhalm et al. 2011).

14.1 Patients

Surgery was conducted on a total of 54 patients who underwent unsuccessful conservative attempts of treatment for at least 6 months prior to surgery with a minimum of 1 month of stationary care in an external clinic. Of 22 of these patients long-term follow-up data are available and will be reported here. The decision for surgery was made in a multidisciplinary conference between doctors, psychologists, and dieticians in close cooperation with the patients and their parents. All patients agreed to participate in a long-term follow up.

Mean patient age ($n = 22$) at the date of surgery was 17.4 ± 2.7 years with a mean BMI of 51.7 ± 8.

Eight patients received a laparoscopic adjustable gastric banding (LAGB). Four of these had to undergo a gastric bypass surgery (GByp) as second procedure due to

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Table 14.1 BMI after gastric banding in eight adolescent patients

Visits with pediatrician and dietitian	Monthly visits in the first year postsurgery, every 6 months thereafter
Blood sampling (Follow-up on: Vitamin A, B9, B12, C, D, E Magnesium, Iron, Phosphorous, Zink, Calcium,. . .Hs-CRP, Lp(a), LDL, HDL, CHOL, Insulin, PTH)	In 1st, 6th, and 12th month postsurgery, every 3 months thereafter
IMT measurement and echohepatography	In 1st, 6th, and 12th month postsurgery, every 6 months thereafter
DXA- and bone density measurement (often impossible: patient exceeding weight limit, etc.)	In 1st, 6th, and 12th month postsurgery, every 12 months thereafter

insufficient weight loss. Fourteen patients primarily received a gastric bypass. All patients received multivitamin supplementation after surgery. Gastric Bypass patients received an additional Vitamin B12 injection (1,800 IE every 3 months). We conducted a strict follow-up routine with monthly visits in our outpatient clinic for the first year. After 1 year visits were planned for every 6 months with quarterly blood sampling during the first year, every 6 months during the second year, and annual testing thereafter. Further measurements included DXA scan for measurement of body composition and bone density, intima-media measurement, and psychological evaluation (Table 14.1). Follow-up data is available for at least 48 months in the LAGB group and at least 24 months in the gastric bypass group.

14.2 Results

14.2.1 Weight Loss

Mean weight loss after 24 months of the patients on which LAGB was performed was 20 $\pm$ 6.3 kg. Interestingly, although initial results were promising, half of these patients showed a regain in weight after approximately 2 years leading to a mean weight loss in the whole LAGB group of only 15.5 kg after 48 months of follow-up. The BMI decreased by 4.8 in the same period of time (Fig. 14.1). It is worth mentioning that these four patients reached or even exceeded their presurgery weight and showed very poor adherence to their postsurgery treatment in our outpatient clinic. Retrospectively, no prognostic socioeconomic or psychological factors could be identified. Gastric bypass was performed as a secondary procedure on those patients whose weight loss was inadequate after approximately 50 months of follow-up. The outcomes are included in the results from the gastric bypass group given below.

In contrast to the LAGB group, all patients who underwent a gastric bypass procedure showed significant and lasting weight loss (Fig. 14.2). The mean BMI

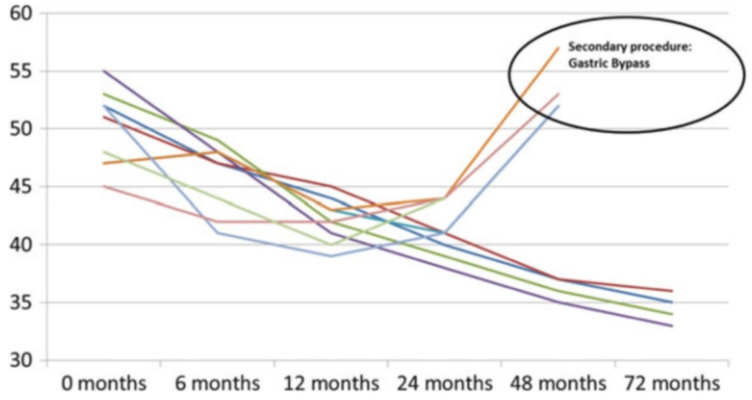

Fig. 14.1 BMI after gastric banding in eight adolescent patients

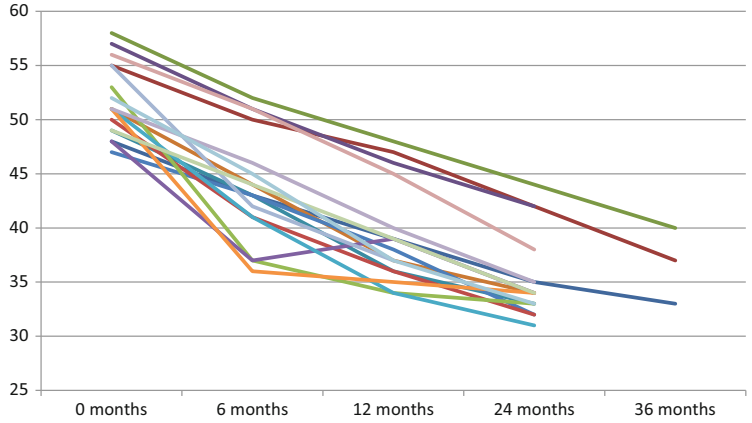

Fig. 14.2 BMI after gastric bypass in 17 adolescent patients

dropped from 51.7 ± 3.4 to 35.5 ± 4.1 in 24 months after surgery, mean body weight changed from 153.9 ± 9.4 to 129.3 ± 7.2.

14.2.2 Vitamin Deficiencies

No deficiencies of micronutrients occurred in the LAGB group. In the Gastric Bypass group 2 transient vitamin A deficiencies, one transient Vitamin B12 deficiency (due to a left out substitution) and five Vitamin D deficiencies (three of

which severe) occurred. One preexisting iron deficiency worsened after surgery was performed. The Vitamin A deficiencies occurred in the 6 months follow-up while the Vitamin D deficiencies manifested mostly after 12 months.

14.3 Discussion

From our experience we suggest the Gastric Bypass as method of choice due to the high risk of weight regain in the LAGB group. Although the initial fears of micronutrient deficiencies from malabsorptive methods are partially legitimate, the LAGB did not seem to be a valid option for the broad majority of severely obese patients. However, it becomes even clearer that prevention and early detection of possible deficiencies is of utmost importance and that long term, or possibly even lifelong follow-up, is a necessity to prevent severe side effects.

Although the rate of severe deficiencies of Vitamin D appears to be shockingly high, a comparison with data from the HELENA-study qualifies this. The HELENA study conducted a large screening in over 1,000 European adolescents and found that, according to current reference levels, 42 % of the otherwise healthy population in pediatric age suffers from a Vitamin D deficiency (Fig. 14.3). Although it is true that the Vitamin D levels decreased in all patients on average after surgery, the distribution of deficient vs. sufficient provision does not largely differ from the HELENA results.

As a conclusion, the Gastric Bypass appears to be an efficient and safe method for weight reduction, provided the procedure is performed at a qualified center by a specially trained multidisciplinary team. Bariatric surgery should still remain an option of last resort and the patient's ability and willingness to comply in a postsurgery therapy and treatment program has to be seen as a *condition sine qua non*.

In our experience bariatric adolescents often show poor compliance to follow-up. Unfortunately, this is an issue reported by almost all work groups performing bariatric surgery but is not well documented in literature. We strongly recommend deploying a patient manager. It would be this person's responsibility to keep track of follow-up visits and, if the patient does not appear, to re-invite him to another appointment. In our experience it was sometimes necessary to make two to three appointments for a patient to show up once.

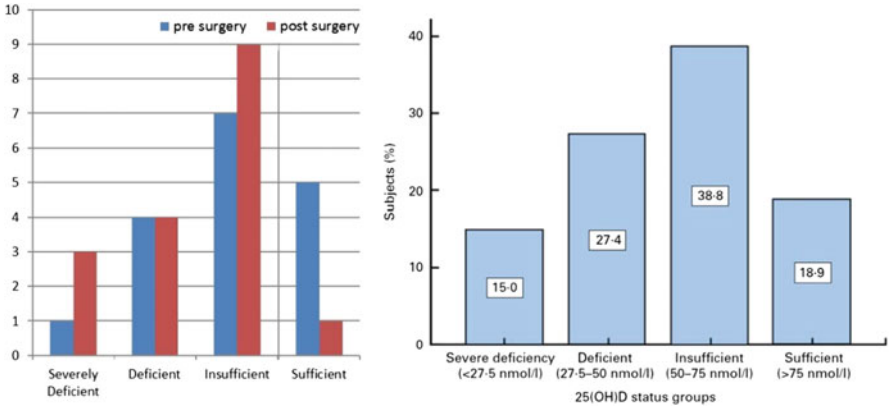

Fig. 14.3 Prevalence of vitamin D deficiency before and after weight loss surgery compared to the European general population (González-Gross et al. 2012)

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Chapter 15
Is There an Indication for BPD-DS/BPD? What the Potential Advantages/ Disadvantages to RYNGB?

Rudolf A. Weiner and Sylvia Weiner

15.1 Introduction

The number of obese and morbidly obese adolescents is increasing in the western industrialized world. Approximately, 7 % of US 18-year olds already meet the definition of extreme obesity and that number is growing every year. In Germany the number of morbidly obese children and adolescents has increased dramatically; 10–20 of the German school children are overweight or obese. But not only the number of obese children has increased but also the weight itself: The annually BMI-gain is in obese twice as in normal weight children. Obesity surgery is not a causal treatment of a disease, but more effective and long-term stable in morbid obesity than conservative treatments (Literatur).

Bariatric surgery in teenagers may avert a number of metabolic problems in later life, according to a retrospective study of obese adults that endeavored to model how their health might have been different had they had bariatric surgery at age 18. The benefits of bariatric surgery in adult obese patients are well known, but data are lacking regarding the outcome of the surgery in adolescents. For the long-term side effects we can expect more severe problems after malabsorptive procedures than in restrictive procedures.

Given that severe obesity is a progressive damaging disease with a 90 % probability to last for life (Guo et al. 2000; Brolin 2002; Christou et al. 2004), the goal should be to prevent the development of irreversible damage and detrimental comorbidities. The risk that surgery could jeopardize a child's normal growth remains the major concern. Better data are needed to determine the best age to intervene and the optimal operation. Some studies have investigated the outcome of Weight Loss surgery and have shown that Weight Loss Surgery in adolescents is safe and associated with significant weight loss, correction of obesity-related

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comorbidities, and improved self-image and socialization (Apovian et al. 2005; Inge et al. 2004a; Dolan et al. 2003; Stanford et al. 2003; Capella and Capella 2003).

Most of the available studies refer to restrictive procedures, such as gastric banding (LAGB) or Roux-en-Y gastric bypass (RNYGB); only few literature and experience are available on malabsorptive procedures such as biliopancreatic diversion (BPD-Scopinaro) or biliopancreatic diversion with duodenal switch (BPD-DS) procedure (Literatur).

However, in contrast to the adult patient the status of physiological maturity is to be respected in the adolescent patient. Neuroendocrine and skeletal maturation are accelerated during adolescence, and the influence of malabsorptive weight loss procedures are not known or described. Generally, it is to be respected that the linear growth spurt occurs before Tanner stage IV in both boys and girls. The majority of skeletal maturity is attained by girls at $\geq$13 years and by boys at $\geq$15 years of age (Inge et al. 2004b).

There are some rare cases of genetic disorders, like the Bardet–Biedl or the Prader–Willi syndrome (PWS), where gastric bypass surgery was successfully proceeded (Daskalakis et al. 2010), but as far as these genetic disorders are rare, these conditions cannot be reported in large series.

15.2 Restrictive Procedures

LAGB and RNYGB are both to be considered as restrictive procedures.

The gastric banding (GB) is the least minimal invasive and reversible procedure with the lowest surgical risk, whereas the gastric bypass was the so-called goldstandard in the USA over more than 2 decades. The different modifications were reduced to the standard proximal Roux-en-Y gastric bypass (RNYGB). The banded gastric bypass, the distal gastric bypass, and the omega-loop gastric bypass are not the first choice and were classified as an expert opinion. In adolescents the "unbanded" RNYGB only should be used. The distal bypass is related to severe protein malnutrition in the long term, and the omega-loop gastric bypass is associated with potential risk of bile reflux and therefore with a gastric cancer risk in the long term of decades.

As far as the recommendation for the use of the gastric band is between ages 18–65, only few published series are available (Dolan and Fielding 2004) In a systematic review and meta-analysis of various bariatric operations in both children and young adults, Treadwell et al. (2008) reported decreases in body mass index (BMI) between 10.6 and 13.7 kg/m^2 3 years after lap-band compared to 17.8–22.3 kg/m^2, 6 years after Roux-Y gastric bypass.

Long-term success of LAGB in adolescent patients is still unknown, but the low morbidity and reversibility of the procedure make it an attractive alternative for severely obese adolescents.

For our experience LAGB is as well as for adults only an alternative for females, because of a higher success rate and better quality of life (Lee et al. 2012).

Both the gastric bypass and adjustable gastric banding result in significant weight loss among morbidly obese multiethnic adolescents at up to 2-years postsurgery.

- For *both boys and girls*
- For *all ethnic groups*

Gagner and his group published the first results of laparoscopic sleeve gastrectomy (LSG) as a first-step procedure in super-obese patients using laparoscopic biliopancreatic diversion with duodenal switch (LBPD-DS). The background for the introduction of this procedure was the high mortality rate of LBPD-DS in patients with BMI >60 kg/m^2, which was 6 %. Later the LSG as a sole bariatric operation or as first-step procedure followed by RYGBP was used for super–super obese patients. In the last 3 years the number of reports and series using the LSG as a single-stage procedure is increasing. The introduction of LSG as a one-stage restrictive procedure in the bariatric field can only be considered if the procedure is standardized and long-term results are available. The size of the sleeve is still under discussion. Another consideration is that because this surgery is irreversible, mistakes should be avoided. This prospective study was undertaken in an attempt to investigate the clinical outcome in relationship to sleeve volume following LSG, while comparing these findings with previously published data of the current purely gastric restrictive operations.

Therefore, the sleeve cannot be recommended for children and adolescents as a single step procedure as far as long-term data is still missing.

In conclusion RYGB is to be recommended (Apovian et al. 2005) as the procedure with the best long-term data and LAGB as the procedure with the least apparent risk for adolescent patients. Because there are currently no criteria to determine which of the two procedures (RYGB or LAGB) is best for any given patient, the decision should rest with the gender of the patient, the patient, the needed BMI-Loss, his or her parents or guardians, and the surgeon and other members of the team (pediatrician, psychologist, etc.) as long as it is not to be described as a genetic syndrome.

In these cases, the most commonly described diseases are the Bardet–Biedl or the PWS.

In our series we have shown feasibility and success in a male patient with Bardet–Biedl syndrome with application of RNYGB (Daskalakis et al. 2010), whereas several reports are published on PWS patients treated with either BPD (Papavramidis et al. 2006) or BDS-Scopinaro technique (Marinari et al. 2001; Brossy 1989).

15.3 Roux-en-Y Gastric Bypass

Sugerman et al. (2003) reported a series of 32 children with a mean age of 16 ± 1 years (range: 12.4–17.9 years) using various operations including gastric bypass with various intestinal limb lengths. The overall EWL was 33 % for a mean follow-up of 11 years (range: 1–15 years) and 18 % "failure" rate, defined as total weight regain.

Capella and Capella (2003) reported an 80 %EWL in 19 children 5 years after a complex gastric bypass of his own comprising vertical banded gastroplasty plus Roux-Y gastric bypass.

Data suggest long-term efficacy and safety of RNYBG in adolescent patients (Treadwell et al. 2008; Spear et al. 2007; Abu-Abeid et al. 2003; Papdia et al. 2007). Similar outcomes have been reported from larger series in adult populations. To date, there have been no negative reports surrounding the use of RYGB in adolescent populations.

Limited data suggest that long limb and distal gastric bypass can also be safe and effective in adolescents (Spear et al. 2007), but they increase the risk of nutrient deficiency and protein energy malnutrition and seem to be most appropriate in superobese adolescents who have reached skeletal maturity.

15.4 Biliopancreatic Diversion with and Without Duodenalswitch

Much data exist on the effectiveness and safety of BPD and BPD-DS in adult populations. Studies report durable excess weight loss of 70–80 % after 14 years. These procedures enable patients to eat a more normal diet without the effects of caloric restriction or dumping. However, these are complex operations, with greater risk of nutrient deficiency and protein calorie malnutrition.

The American Society of Bariatric Surgeons currently recommends that BPD and BPD-DS be performed only by experienced surgeons with a commitment to long-term follow-up.

The effects of BPD and BPD-DS in adolescents are unknown. Until reliable long-term data are available, this malabsorptive procedure is not considered an appropriate option for adolescent WLS patients.

The largest series ($n = 68$) with the longest follow-up, a mean of 11 (range 2–23) years, was reported by Papdia et al. (2007). They used a BPD with distal gastrectomy and 50 cm common channel.

They reported 78 % excess weight loss (% EWL) at the cost of protein deficiency (16 %), reoperations (13 %), and long-term mortality (5 %). It is not clear whether their results have improved over time.

15.5 Malabsorptive Procedures in Patients with Prader–Willi-Syndrome

In PWS, mental retardation and compulsive hyperphagia cause early obesity, the comorbidities of which lead to short life expectancy, with death usually occurring in their 1920s. Long-term weight loss is mandatory to lengthen the survival; therefore, the lack of compliance in voluntary food restriction requires a surgical malabsorptive approach. Application of a restrictive procedure (especially LAGB, but RNYGB, too) can lead to a high rate of complications like staple line disruptures, band slippage, and others. Pure malabsorptive procedures like the distal gastric bypass or even jejunal bypass can lead to severe malnutrition, even with the consequence of death due to the incapability for compliance of the patients (Brolin 2001; Faintuch et al. 2004).

15.6 Biliopancreatic Diversion

Marinari et al. (2001) described: 15 PWS patients treated with BPD and followed (100 %) for a mean period of 8.5 (Apovian et al. 2005; Inge et al. 2004a, b; Dolan et al. 2003; Stanford et al. 2003; Capella and Capella 2003; Daskalakis et al. 2010; Dolan and Fielding 2004; Treadwell et al. 2008; Papavramidis et al. 2006) years.

No perioperative complications were observed. Percent excess weight loss (%EWL) was 59 ± 15 at 2 years and 56 ± 16 at 3 years, and then progressive regain occurred; at 5 years %EWL was 46 ± 22 and at 10 years 40 ± 27.

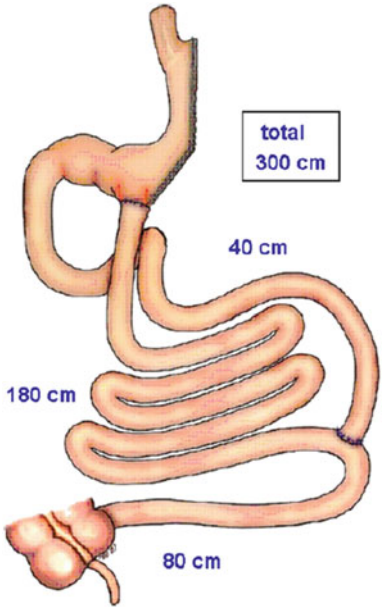
Therefore, they concluded that BPD has to be considered for its value in prolonging and qualitatively improving the PWS patient's life, whereas Grugni et al. (2000) reported severe reduction of bone mass density, hypochromic anemia, hypoproteinemia, and diarrhea associated with eating and therefore did not recommend the procedure for this kind of patients. Therefore, the results of Larrad BPD need to be analyzed, as even in long-term follow up of 10 years Larrad's BPD has shown good results in terms of weight loss and quality of life, a low rate of metabolic sequelae, including hypoproteinemia rate <0.5 %, and a revision surgery rate of 0 % (Larrad-Jiménez et al. 2007).

15.7 Duodenal Switch

Marceau et al. (2012) were describing in 2010 their center's experience with the duodenal switch procedure in 13 obese adolescents including those with PWS. Previous authors have noted that the use of the duodenal switch procedure cannot be recommended for most adolescents due to the adverse risk-to-benefit ratio (Miyano and Inge 2008).

15.8 New Procedures

In 2003, Santoro proposed a new surgical strategy for extreme obesity that utilizes a novel combination of different preexisting surgical procedures. The theoretical and physiological bases for this surgical strategy, as well as surgical outcome results, were recently reviewed. The Santoro III technique consists of a laparoscopic sleeve gastrectomy and enteroomentectomy, which reduces gastric capacity to about 150 ml and the small bowel length to 3 m, preserving the distal small bowel (Santoro et al. 2003, 2008; Manoel 2010).



15.9 Gender

Like in adults gender seems to play an important role in the choice of the procedure in adolescents, although no true algorithm could be stated (Figs. 15.1, 15.2, and 15.3).

On basis of the outcomes of the Designated Bariatric Surgery Centers of Excellence's Bariatric Outcomes Longitudinal Database (BOLD) De La Cruz-Munoz stated in 2011 on the IFSO World Congress in Hamburg (De la Cruz Munoz 2012) that obesity surgery has the potential to be an effective treatment option for significant weight loss in US adolescents, irrespective of gender or ethnicity.

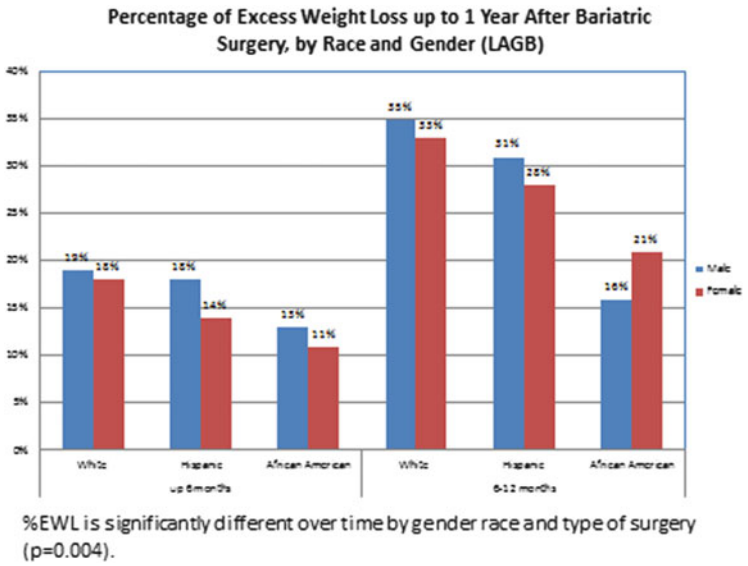


Fig. 15.1 Influence of race and gender in obesity surgery in adolescents 1 year follow-up after gastric banding (De la Cruz Munoz 2012)

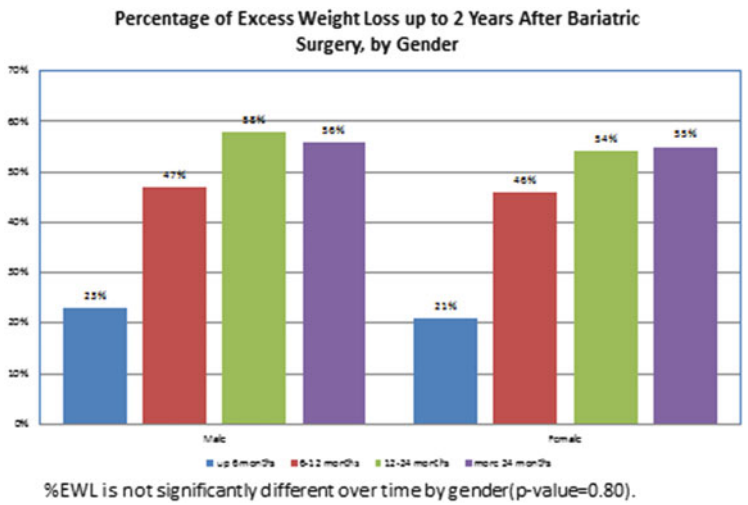


Fig. 15.2 Influence of race and gender in obesity surgery in adolescents 2 years follow-up after gastric banding (De la Cruz Munoz 2012)

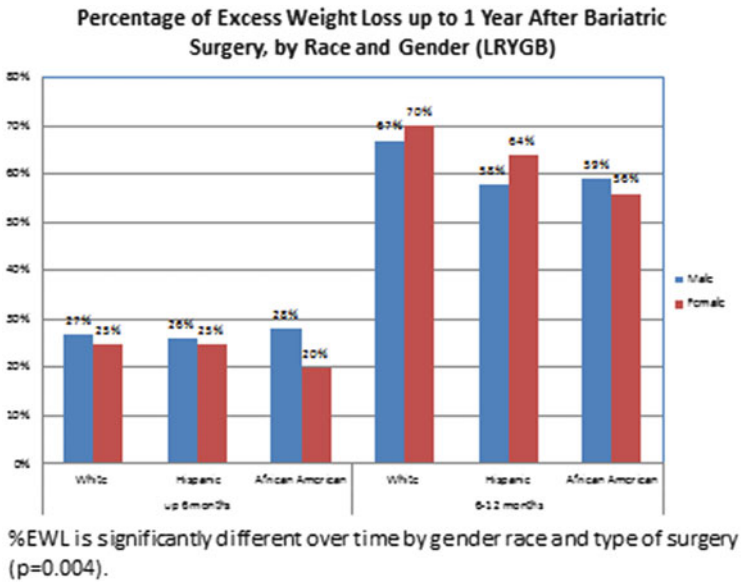


Fig. 15.3 Influence of race and gender in obesity surgery in adolescents 1 year follow-up after gastric bypass (De la Cruz Munoz 2012)

15.10 Own Results

In our own series we had 35 patients under 18 years and 40 patients in between 19 and 20 years. In the total series of 75 were 51 female and 24 male. The BMI classes were shown in Table 15.1 und the procedures in Table 15.2.

The mortality rate was 0 % with no occurence of minor or major complications. The reoperation rate was related to band procedures only. In the first time period from 1994 to 2000, the band was the dominating procedure in Germany and therefore all adolescents were treated with adjustable bands. From 29 bands a total number of 14 were removed within 5 years. Twelve patients were converted to other procedures later.

After the year 2000 gastric resections were introduced into the field of obesity surgery in Germany too. Especially in young female with lower BMI (<45), the band were and are still the first choice.

The mean excess weight loss was shown in Table 15.3 (excess weight loss in %) for the time interval up to 2 years after surgery.

The number of type 2 diabetes in the age below 18 years was 3. Two patients were under insulin treatment (both 15 years) and one was treated by metformin (1,000 mg) per day.

All patients were free of insulin and oral medical treatment from the time point of surgery. All blood sugar levels normalized within 24 h. All diabetics were treated by RNYGB.

Table 15.1 BMI classes and age

BMI	*n* (89)	<18 age	19–20 age
<40	14	8	6
>40 < 50	43	26	17
>50 < 60	24	11	13
>60 < 70	8	4	4
>70	0	0	0

Table 15.2 Procedures in the time period 1994–2000 and 2000–2012

Period	1994–2000	2001–2011
BPD-Scopinaro	0	2
BPD-DS	0	1
LAGB	14	15
RNYGB	0	10
Sleeve	0	4

Table 15.3 Mean excess weight loss 1 and 2 years after surgery

Procedure	EWL 1 year (%)	EWL 2 years (Inge et al. 2004a)
Gastric banding	64 %	66 %
Gastric bypass	78 %	79 %
BPD	64 %	76 %
BPD-DS	88 %	90 %

From 14 removed bands two patients gained their weight and were not available for a second procedure. The reason for band removal was the impaired quality of life caused by the restriction. From 12 reoperated patients received one new band only (re-banding for material defect). Ten patients were converted to RNYGB. One patient developed 10 years after gastric banding with successful weight loss a band migration and was converted to BPD. The another indication for BPD was seen in a patient with PWS. The case with the BPD-DS came from Ireland with BMI 53 and was 18 years. The female patients had a band in history and three family members had a very successful BPD-DS in our department. She was well informed and so far the indication was the patient intension. The outcome 8 years after surgery is still excellent with EWL of 96 % and the lack of deficiencies.

15.11 Discussion

The laparoscopic obesity surgery in high-volume centers is safe and effective. The surgical risks are very low, but with placements of artificial foreign bodies like the adjustable gastric band, the reoperation rate increases with time. The placements of adjustable bands are bridging procedures from adolescent to adult age. After intermittent effective weight loss and improvement of comorbidities, the patient can make his own decision in the stage of an adult by himself. Therefore, the band is

still an acceptable indication for obesity surgery in adolescents, especially in female.

Furthermore, several publications have reported successful outcomes for prevention and treatment of obesity in PWS with dietary intervention including reports of severely obese adolescents and young adults (Schmidt et al. 2008; Messersmith et al. 2008). In addition, the advent of growth hormone therapy has led to increased stature, muscle mass, and reduced fat mass for individuals with PWS diagnosed at an early age in lieu of surgical procedures in those affected with this genetic disorder. These results and our own personal experiences caring for individuals with PWS over many years directly contradict the conclusions of Marceau et al.

The data presented by Marceau et al. provide further support for the conclusions of a recent review article that bariatric procedures have an adverse risk-to-benefit ratio for treatment of obesity in individuals with PWS and should be regarded with significant caution and trepidation. Although bariatric procedures may produce weight loss in individuals with PWS, the need for continuous monitoring of nutritional status/restriction of food intake during the early postoperative period as well as subsequent years remains present to avoid weight regain. Treatment regimens involving supervised reduced-energy diets with vitamin/mineral supplementation, restricted access to food, daily exercise programs, and approved growth hormone therapy are both safe and therapeutically efficacious. Sometimes the BPD can fail in these patients with monogenetic diseases too (De Almeida et al. 2005). Our own experiences in cases of Laurence–Moon–Bardet–Biedl syndrome with gastric bypass are positive. The glucose regulation improved within 2 days and all comorbidities like hypertension, asthma, triglycerides, and others improved. The patient showed an excess weight loss of 68 % up to 5 years and is still under control at a specialized University hospital.

In general, the monogenetic diseases are rare in comparison to the increasing number of overweight and morbid obesity in children and adolescents and should be treated in specialized centers earlier. The surgery for obesity is one effective and safe option after failure in conservative treatment. The surgery as an effective treatment option in obese adolescents becomes more and more importance all over the world.

Inge (2012) analyzed retrospectively at 1,492 morbidly obese adults who were seeking bariatric surgery in the USA to determine whether their comorbidities later in life could be associated with their teenage body weight. At the time of the study, the median age of his subjects was 17. Their adult BMI was 46 kg/m^2, whereas their age-18 BMI, based on participant recollections, had been 26 kg/m^2. In multivariate analyses, weight status at age 18 emerged as a key predictor of adult disease, including renal disease, diabetes, hypertension, venous stasis, and other end points (Table 15.4). The study has shown that obesity surgery in teenagers may avert a number of metabolic problems in later life. The risk factors are listed in Table 15.4.

These date led directly to the question: why we do not start the surgery intervention earlier in obese with morbid obesity and metabolic syndrome in adolescents? The effects of the surgery for obesity are more effective in younger population than in older one.

Table 15.4 Adolescent weight status is a predictor of future disease (Inge 2012)

Future disease	Adjusted relative risk
Renal disease	5.82
Diabetes	1.37
Hypertension	1.23
Venous stasis	6.39
Walking limitation	4.34
Asthma	1.47

15.12 Conclusions

Obesity surgery in adolescents is effective and safe, but need special support and to be followed up very closely, especially girls at risk for pregnancy. With rigorous follow-up and supplementation, results are better than commonly achieved in adults. Sustained weight loss is substantial, and deficiencies are rare and marginal. Our experience is limited to adolescents 12 years of age or older, whom we have found to be responsible and mature. Severe obesity is so damaging at this age that we agree that surgery should not be delayed. Reversible restrictive procedures are the first choice, especially in female. Gastric bypass has an excellent risk–benefit ratio. Malabsorptive procedures, like BPD with or without duodenal switch, should be limited to monogentic obesity, like PWS. In monogenetic diseases failures after malabsorptive procedures were seen as after gastric bypass as well. If a BPD is scheduled, than for prevention of protein deficiencies the Larrad modification should be used. The BPD-DS has a higher surgical risk, but it allows normal eating habits. Obesity surgery improves the quality of life of the patients and their parents. The situation for lifelong vitamin and calcium supplementation should be tested upfront surgery.

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Chapter 16
Psychological, Nutritional and Sports-Scientific Aspects of Obesity in Adolescence

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16.1 Introduction

Meta-analyses show that weight loss through conservative therapy and prevention does not indicate any big changes (Ebbeling et al. 2002; Miller and Jacob 2001). What is it specifically that makes it so difficult for obese adolescents to lose weight and puts so much stress on their life?

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16.2 Psychological Effects and Co-morbidities

16.2.1 Discrimination and Quality of Life

Obesity in itself conveys a good message: We have enough food to eat, and no hard physical labour is required to obtain it. Having said that, the image we have of the messengers, namely obese adults and children, is the very old one of fat people guilty of—the sin of—gluttony. These people are regarded as being lazy, stupid and weak-willed and face discrimination in the workplace and when looking for a partner (Friedman and Brownell 1995; Stunkard and Sobal 1995; Doll et al. 2000). Our beauty ideal of being thin and, from the 1980s, constantly even thinner has added to this difficulty. This has affected young people in particular, who already feel insecure during puberty and who yearn to be part of the in-crowd and to be liked and accepted by peer groups. Discrimination against "fat" adolescents is high (Moens et al. 2005); their quality of life is not only poorer compared to those with normal weight (Must and Strauss 2000; Bauer 2006) but even worse than that of children suffering from cancer (Pinhas-Hamiel et al. 2006; Schwimmer et al. 2003). Even adolescents who are able to handle their obesity well, rate those areas of their quality of life that relate to overweight as extremely negative, for example buying clothes, handling of teasing or hurtful remarks during visits to doctors and job interviews (Ardelt-Gattinger and Meindl 2010).

16.2.2 Body Image and Eating Disorders

As far as the desired body image and how they rate pictures of bodies of different weights are concerned, there is no major difference among adolescents of different body weight categories: The "fat one" is the ugliest, and the slim one is the most beautiful, and one would like to look like her. The dream of having the body of a model plays an important role, and diet has countless times been advocated as the way to get there (Ackard et al. 2002). This is conducive to the fact that young people with a BMI percentile of 97 and more are equally co-morbid with eating disorders as obese adults. While it is assumed that about 30 % of adults suffer from binge eating disorder and 7 % from bulimia (Herpertz and de Zwaan 2008), according to a representative Austrian sample of young people between 10 and 18, these values are respectively approximately 24 and 9 % for adolescents (Ardelt-Gattinger and Meindl 2010). Studies based on a new questionnaire on pre-clinical eating disorders carried out on 4,400 children and adolescents in the age group between 10 and 18 additionally revealed that these show so-called pre-clinical (Bulik et al. 2000; De Zwaan et al. 1995; Dingemans et al. 2002) eating disorders, namely "preoccupied with weight and shape" and "pre-clinical vomiting", at a very early stage. The latter refers to self-induced vomiting when a person has the subjective feeling that he or she ate too much, however, is not done as much and

as regularly as in binge eating according to the definition of DSM IV. Even here, obese people differ significantly from other weight groups.

16.2.3 Mental Disorders

Since the beginning of obesity research, mental disorders have been discussed as causes and effects of the disease. Meta-analyses provide a conflicting picture. The reported differences between people with normal weight and obese people in respect of fully developed anxiety disorders or depression, for example range from none to significant. Studies indicating mental disorders as a contributing cause of obesity are quoted, as are others that regard these only as after-effects (Britz et al. 2000; Wabitsch et al. 2005; Mata and Munsch 2011).

The problem is mainly due to the fact that intervention, cross-sectional and longitudinal studies of clinical and representative samples are frequently compared in an impermissible manner, but also due to the fact that the determination of data from longitudinal studies for adolescents is methodically difficult. On the one hand, they show significant mood swings caused by developmental psychological factors, while on the other hand, at the time of an initial examination—similarly to the area of eating disorders—one can expect to find pre-clinical symptoms rather than the fully developed disorder.

Accordingly, the literature agrees that the conflicts and noticeable problems at an emotional and behavioural level reported by obese adolescents and their parents largely correspond (Ender et al. 2011). In respect of the global depression score, Moens et al. (2004) found virtually no differences between obese and normal-weight adolescents of either sex. In fact, they were able to explain 42 % of the total variance determined in the Children's Depression Inventory with more negative self-evaluations of obese children and adolescents in respect of their self-concept (particularly in the athletic field). Similarly, Boutelle et al. (2010) demonstrated that girls who, during their first examination, were found to be obese later developed very frequent symptoms of depression, which, however, did not fulfil a clinical fully developed dysthymia or major depression.

This tendency is also suggested by a more recent meta-analysis that, quite correctly, is only based on longitudinal studies. It suggests a very plausible "bidirectional connection" (Mata and Munsch 2011) of processes that systemically influence each another; however, the effects of which are not particularly pronounced in adolescents (Luppino et al. 2010).

Irrespective of the discussion on the general significance of the differences and the cause or effect of mental disorders, and against the background of the degree of stigmatisation mentioned above, a differentiated diagnosis of obese adolescents using at least a screening method appears to be appropriate, also in the interest of prevention.

Boutelle et al. (2010, p. 296) quite rightly mention the possibility that the body weight status may act as a "factor along the pathway of development of depression

in some adolescents". The unfavourable developments experienced in the private and work environment (Pitrou et al. 2010) mentioned above and known from numerous studies should be countered by prevention and health promotion. Hebebrand (2009) additionally points out that obese adolescents who diet are particularly vulnerable to developing fully developed mental disorders and that, against this background, we have to critically examine therapy programmes for children and adolescents.

16.3 Mental Control Variables of Diet and Physical Activity

16.3.1 Obesity: An Addiction we Cannot Completely Abstain from

But also obese people who are not on a diet state that they have strong craving for overeating. This should not be understood as the craving for sweet or fat, but simply for excessive eating, which, as far as the intensity of the desire is concerned, does not differ from other addictions such as alcohol or nicotine dependency, compulsive gambling or even addiction to sports (Ardelt-Gattinger et al. 2000a, b, 2003; Franke 1995). These studies, which were carried out using parallel questionnaires, have recently also been confirmed by neurophysiologic investigations. According to these, obese people have a deficiency of dopamine receptors similar to that of people addicted to heroin and alcohol (Wang et al. 2004; Volkow et al. 2002).

Nine independent studies have shown that the same holds true for children and adolescents of the age group between 8 and 18 (Ardelt-Gattinger and Meindl 2010, 2011a, b). Also in children/adolescents, craving for and addiction to overeating fulfil the three minimum criteria for the diagnosis of an addition as defined by the international diagnostic schemes ICD 10 or DSM IV. The extent of the addiction very significantly distinguishes obese children from all other body weight categories, and this is an important factor influencing increase or decrease in weight both in in-hospital and out-patient weight-loss programmes. Adolescents who stated that they had high food craving showed an increased activity in the hippocampus and the insula—the regions of the brain associated with addiction (Liebmann-Wallner et al. 2010; Pelchat 2002)—when they were confronted with low-calorie foods. Besides, a correlation exists with the high fasting insulin levels that are characteristic of obese people (Young et al. 2000).

The dramatic situation of obese adolescents in respect of these variables may be summarised by stating that we cannot completely abstain from food. Living in a rich affluent society with abundant advertising for unhealthy food, they find themselves in an almost hopeless situation.

16.3.2 Control, Thought Suppression and the "Ironic Processes" of the Brain

Following the recommendations to lose weight, as advocated by consultants from all disciplines worldwide, requires control. But in fact, excessive control on eating, so-called "restrained eating", is, on the one hand, part of the eating disorders mentioned above, while on the other hand, the values of obese adolescents in respect of this variable are *higher* than for other body weight categories (Ardelt-Gattinger and Meindl 2010). Previously, it was assumed that there was a more positive—"moderate"—control that a person could learn. Neurocognitive studies and cognitive research open up a new approach that is based on the theory of thought suppression (Wegner 1994; Stroebe 2002). "Control", with its extreme form of "restrained eating", is the meta-level, so to say, that describes how a person handles or would like to handle the problem of excessive eating. Relevant items from the questionnaire compiled by Pudel and Westenhöfer (1998) "I try to eat less during meals..." illustrate this. The theory of thought suppression, on the other hand, provides a model that describes how the perceived or actual confrontation with food or meals takes place. It can be demonstrated that the human brain is principally unable not to NOT think about something. Instead, every "control" thought, like "I am NOT eating chocolate and chips now", activates the image of the chocolate, etc. in the brain, similar to a search command on the PC for "Search "NOT obesity" that will open all files and text passages in that the word is found.

We can only suppress thoughts. According to the *Theory of Ironic Processes of Mental Control* (Wegner 1994), this process of thought suppression is based on the interaction of a conscious "operating process" (OP) and a non-conscious "monitoring process" (MP). The interaction of these two control processes in the brain in conjunction with continued thought suppression can produce "deep cognitive activation", i.e. a non-conscious activation of the thought to be suppressed. The action of the OP is a function that was acquired late in the history of humankind and that consumes a great deal of cognitive resources. Any form of distraction, fatigue, stress, etc. thus leads to a deterioration of the OP and to a corresponding increase in the accessibility of the non-desired thought.

Consequently, the suppressed thoughts become even more conscious through so-called "ironic processes", which will in turn control the behaviour towards eating, and even binge eating. In an initial experiment, it was shown that adolescents who, at the sight of their favourite snacks, were instructed to suppress the thought, produced significantly more saliva than those who did not receive this instruction (Meindl et al. 2010).

Another study carried out by Erskine and Georgiou (2010) produces the connection to the term "control" mentioned above. They were able to prove that "restraint eaters"—the category in that most obese adolescents fall—under the condition of thought suppression, thought more of chocolate and ate more of it than those with lower control levels. This proves that the pathogenic approach

followed in the past by diets and "control as much as possible" is counterproductive.

16.3.3 Disinhibition and Emotional Eating

According to the original concept of Stunkard and Messick (1985) and the subsequent studies carried out by Pudel and Westenhöfer (1998) and Grunert et al. (2010), the variables disinhibition and emotional eating were shown to depend on control. The higher the control, the higher the "disinhibition", i.e. the temptation to eat by looking at and smelling of snacks, and "emotional eating" out of frustration, anger, stress and boredom, for example. The new approach of controlling in the sense of thought suppression should not change anything about these interrelations.

16.3.4 Lack of Salutogenic Thought Patterns

From other areas of therapy and prevention, we know that in principle, salutogenic thinking is more successful than pathogenic controlling. As discussed above, obese adolescents have elevated levels in the latter and as expected, show a deficit in salutogenic cognitions such as enjoyment of eating, focus on healthy food, etc. Values on a questionnaire on salutogenic eating and physical activity show that these values decrease with increasing weight of adolescents (Ardelt-Gattinger and Meindl 2010). However, the processes explained under Sect. 16.2.2 clearly indicate that a paradigm shift towards a salutogenic approach is required in prevention and therapy. Apart from the corresponding interventions oriented towards the systemic therapy, the new paradigm of "Health @ any size" represents the required basis for this.

16.3.5 Motivation to Exercise and Physical Fitness

There is no question that, apart from the amount and type of food we eat, the fitness gained through exercise and sports is the most important predictor variable of overweight, obesity and the medical co-morbidities associated with these (see also: Korsten-Reck et al. 2005; Ring-Dimitriou 2007). Thus, motivation to exercise is an important cognitive control variable. The common distinction between intrinsic and extrinsic motivation (Ryan and Deci 2000) defines the prediction of the behaviour and the corresponding physical fitness.

The term extrinsic motivation is used when the action is performed mainly due to external consequences and—which is often forgotten—is stopped when the

person fails to receive such positive confirmation from the environment. Extrinsic motivators mentioned in the literature include health and weight loss or the positive supporting influence of peers and family. The result of the action is normally considered more important than subjective feelings and thoughts (Pedersen 2002). If we investigate these in detail, it becomes evident that they are more susceptible to failure than intrinsic factors.

Using health and weight loss as motivation is additionally associated with age-specific problems since children and adolescents not always experience or perceive the effect directly. In addition, especially for adolescents, health is not yet a relevant term. Obviously, in children, the motivational significance of experiences of nature, just like the other mentioned factor of positive influence of peers and family, depends on age and social class (Oerter and Dreher 1995; Dollmann et al. 2007).

The intrinsic factors that motivate due to inner satisfaction have a more stable impact on pursuing the behaviour for its own sake (Ryan and Deci 2000). Pleasure and enjoyment of physical activity are most important in this regard, but also feelings of excitement or challenge, which are rated as significant by almost 50 % of adults and are the motivating factor per se for children and adolescents (Wilson et al. 2005). However, the perception of what is fun about physical activity differs to a great extent. According to a European study, "to be able to perform physically" (physical performance) is another motivator for regular physical activity among children/adolescents, which among adults is already ranked second after health (TNS Opinion and Social 2004).

Studies have shown that the extrinsic motivation for movement, "I should, I must..." is higher in obese adolescents than in people with normal weight (Ring-Dimitriou et al. 2010b). This is plausible, because everybody tells them that they can lose weight through exercise. However, studies have also shown that it is primarily the intrinsic motivation to become physically active, thus "I want to, I can...", what is associated with actual fitness to a significant extent. The extrinsic motivation, on the other hand, is not but is instead correlated with pre-clinical eating disorders—also to a significant extent (Ring-Dimitriou et al. 2010b).

The intrinsic motivation to become physically active is significantly lower in obese adolescents than in all other body weight categories. It is understandable that a child's natural intrinsic "motor" of fun and enjoyment of exercise, being able to perform or to be fit, cannot be started when the visible fat moves as well prompting others to start teasing them, and that enthusiasm for sports—mostly associated with humiliating school sports—is relatively limited.

As far as physical fitness is concerned, almost all physical fitness test battery of the AD-EVA (exercises such as "pull-ups", "standing broad jump", "hurdle boomerang run" or "six-minute run") showed significant decreases in the respective test performance with increasing percentile groups (Ring-Dimitriou 2007). This is consistent with results that show a negative relation between physical fitness, particularly endurance (e.g. 6-minute run), lower (standing long jump) and upper body strength (holding the slope or pull-ups) with variables such as BMI, waist circumference or the sum of skinfold thickness (Brunet et al. 2007; Ring-Dimitriou

et al. 2010a). This, however, does not apply to all motor tasks of the PFTB. For example, the differences among percentile groups were not as pronounced for tasks such as the 20-m run and the jump-and-reach test. In these tests, no significant differences between those in the high to normal-weight range and those who were overweight were found. The effect of the body weight was even less significant in motor test that primarily assess coordination under time, agility or endurance (i.e. lateral jumping) as the group of underweight to normal weight did not differ significantly from the high-normal weight or the overweight group. The result of this motor tasks implies that handling the coordinative stress and the acceleration of the body part masses appear to have a greater influence than overcoming the gravitation—including the 90th percentile. Only in obese children test performance was affected by body weight.

In the literature, the differentiated results represented above have yet been discussed or, in most cases, have not been tested in a "fair" manner, since the performance of obese people is compared to that of normal-weight people. This has certainly contributed to the fact that the potential for physical activity in obese adolescents is often underestimated. Obese children and adolescents can manage motor tasks with as much ease or difficulty as those with normal weight, as the analysis of the test criteria *level of difficulty* and *level of discriminant power* revealed for the test items of the PFTB (Ring-Dimitriou et al. 2010a). It is therefore essential to distinguish between "the ability to solve a motor task" and "the performance as an outcome of executing the motor task". It could also be shown that bi-weekly exercise programmes aimed at intrinsic motivation and focussing on the strengths of obese adolescents and on helping them deal with their weight-related weaknesses, brought about a significant increase in motor performance levels within 1 year (Also see Ring-Dimitriou 2006; Birnbacher et al. 2009).

The results can be summarised by stating that future programmes for obese children and adolescents should be aimed more at maintaining and/or improving motor skills. In order to reduce the increase in childhood obesity, it is not sufficient to aim at a specific amount of physical activity, set at 60 min. of moderate to strenuous activity daily (Titze et al. 2010). The focus has to be on "solving motor tasks", as positive effects can be achieved more rapidly.

16.3.6 Dietary Preferences

As mentioned above, the pathogenic multi-causality of obesity can be summarised in the formula "Move more, eat less and healthy". In addition to the excess food intake (that can be influenced only little), unfavourable food choices also need to be addressed. As far as the latter are concerned, obese adolescents do not differ significantly from adolescents with normal weight, as frequency questionnaires have shown (Pudel and Westenhöfer 1998). Preferences for a "healthy" diet would be desirable in all body weight categories: particularly a higher consumption of fruit and vegetables (while simultaneously reducing fats and sugar) and replacing

sugary drinks with no-calorie drinks (water). There is also evidence that lowering the glycaemic load by increasing the proportion of wholemeal products or reduction of foods "tolerated" in normal-weight persons can have positive effects for obese adolescents (Kerstin 2009; Wabitsch et al. 2009).

Even though studies on dietary preferences of the cohort mentioned at several places above have shown significant differences in preferences for "healthy" or "fatty" food and "snacks", the difference in the strength of the effects is rather minor, meaning that, also in respect of preferences, we could cite unfavourable behaviours in general, which are only to a limited extent specific in obese adolescents (Kiefer et al. 2010). According to a meta-analysis of 17 studies involving over 180,000 children and adolescents, obese children and adolescents differ from normal-weight children and adolescents only in terms of their concrete eating behaviour in the—protective—aspect of shared meals (Hammons and Fiese 2011).

16.4 Changes in Psychological Variables

To date, the change in the quality of life has primarily been measured in terms of the weight loss, and it has been shown that the latter changed dramatically for the better (Treadwell et al. 2008; Cremieux et al. 2010). Initial results obtained with conservative therapy groups of adults and adolescents suggest that the above control variables of eating behaviour and physical activity can be influenced positively by conservative interventions, particularly by cognitive behavioural therapy. In this regard, "addiction to overeating" was found to be the strongest predictor of weight loss (Ardelt-Gattinger et al. 2003, 2011a).

The results obtained in an initial evaluation carried out 18–24 months after surgical interventions (gastric banding and gastric bypass) with the entire test system measured using above-mentioned variables was surprising: 60 male and female patients aged between 20 and 65, including 10 adolescents between 15 and 18 years, for both OP procedures changed significantly towards more favourable values in respect of eating and exercise cognitions or respectively higher quality of life and lower values of eating disorders. Only five scores, namely those for "control", "food enjoyment", "bulimia", "over-concern with weight and shape" and "preferences for a healthy diet" remained the same. No negative changes were recorded at all.

Bypass patients showed even significantly more favourable results in some post-op values. With respect to eating disorders, a reversal could be recorded: Male and female bypass patients had higher pre-surgery values, whereas after surgery, all of them could be considered cured from binge eating disorder and bulimia. Seven gastric banding patients developed the fully developed bulimia (Ardelt-Gattinger et al. 2011b). This result is important considering the fact that gastric banding is recommended as the lower-risk surgery especially for adolescents, at least in view of getting an accurate *post*-operative diagnosis and individual assistance and therapy if required. Interdisciplinary diagnosis is recommended before surgery,

and sometimes even stated as a prerequisite, while at present, it is not done after surgery.

16.5 Summary

Numerous mental control variables of eating behaviour and physical activity and also specific effects of their disease on the quality of life exist that are typical of obese adolescents. Dietary preferences of obese and normal-weight adolescents do not differ significantly. Physical fitness is often analysed in a too "unfair" (as it is not compared to the body weight reference group but rather to the normal-weight group) and undifferentiated manner, and its opportunities are underestimated.

The data supported by results from questionnaires of a large cohort of adolescents and confirmed by additional longitudinal studies and experiments, and even some neurocognitive research work, is not inconsistent with previous assumptions. The effect of high eating control—the most thoroughly researched area to date—however, should be seen in a new light. These "ironic" processes of cognitions controlling the eating behaviour and physical activity require new approaches in health communication, counselling and therapy. Like all other interventions, appropriate post-operative care should be developed for surgical treatment of adolescents as well.

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Chapter 17
Current Guidelines of Bariatric Surgery in Adolescents

Martin Fried, Karin Dolezalova, and Petra Sramkova

17.1 Introduction

17.1.1 Brief Epidemiology of Childhood and Adolescents Obesity and Its Consequences

For rather a long time, obesity problem in adolescents and children was largely ignored, or at best underestimated. This applies to both the potential health consequences and obesity tracking in adulthood and effective treatment.

The magnitude of childhood obesity is, however, striking, thus substantially negatively impacting social, economic, and health status of adults as well as the heathcare systems in most of the European and other countries worldwide. In more than half of European Union countries, the prevalence of excess body weight (including obesity) exceeds 15 % in adolescents, regardless of their gender. This situation is even worse from global, worldwide perspective. Thus, more than one-fifth of adolescents and children have their BMI index above the 85th percentile (Troiano et al. 1995; Okamoto et al. 1993). Even worse, around 10 % of children have body mass index above the 97th percentile. This in fact means that they reached true obesity range according to age- and gender-adjusted percentile (Dietz 2004; Flodmark et al. 2004; Pi-Sunyer 1991).

It has to be stressed, however, that definition of overweight and obesity in children and adolescents is not as standardized as in adults. There are several

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reasons why it's more difficult to firmly diagnose obesity and overweight in children and adolescents as they are physiological variations in body composition, caused by greater natural age- and gender-related differences. This may bias distinguishing between physiological adiposity and excessive one. Therefore a proper diagnosis of obesity in childhood may be indeed much more difficult.

For screening purposes anthropometry including skinfold thicknesses seems to be among the most practical and easy to obtain methods. However, it has to be taken into account that the BMI, Body Mass Index/weight (kg): height (m^2)/and skinfold thickness measurements may vary in their sensitivity and specificity, especially when comparing different epidemiology reports and studies (Guillaume 1999; Zimmermann et al. 2000).

Therefore very important and really alarming is the time-trend comparisons in obesity prevalence in the age groups of adolescents and children. There has been annual increase in the prevalence of childhood obesity. The growth observed is steadily rising and nowadays is actually tenfold higher than it was in the 1970s of last century.

Generally speaking the fatter the child, the higher the relative risk of becoming a fat adult (Power et al. 1997a). Moreover, massive obesity which is present in the second decade of life span of the adolescent individual, especially if both parents of such an individual are obese as well, has a strong prediction of adulthood obesity (Power et al. 1997b; Serdula et al. 1993; Whitaker et al. 1997). These data should be of a specific concern from societal, economical, and health points of view. Obesity reduces quality of life and life expectancy. Obesity in adolescence is associated with significant health risk and increased rates of premature mortality in adult life. In Europe it's estimated that mortality attributable to excess weight may be as high as almost 8 % of all deaths (Banegas et al. 2003). Unfortunately, obesity does not mean only a simple growth of fat mass and excessive fat storage. There are serious, obesity-related, and triggered diseases, namely type 2 diabetes mellitus, dyslipidemia, hypertension, sleep apnea, and many others which are excessively prevalent in obese adolescents and later in adulthood result in metabolic, cardiac, renal, ophthalmic, and many other medical and social complications (Schwimmer et al. 2003; Wang and Dietz 2002). This is becoming critical, for example, in worldwide dramatically increased prevalence of type 2 diabetes mellitus. In the USA it's estimated, that about 30 % of children born since 2000 will develop type 2 diabetes mellitus during their life, and about 50 % out of all Hispanic and African American children born since 2000 will develop T2DM (Fact Sheet 2005).

Weight loss in adolescents has proven to be associated with similar benefits as weight loss in adulthood. Weight loss decreases coronary disease risk factors as well as risks of other obesity-related mortality in adults. Effects of weight loss depend on life time when achieved, ideally if weight loss is achieved while still in adolescence (Mossberg 1989; Abu-Abeid 2003).

17.1.2 Role of Bariatric Surgery

In the past two decades bariatric surgery has proved to be the most effective treatment for morbidly obese patients both from efficacy and durability point of view. Recent long-term studies show that there is a substantial reduction in mortality after bariatric surgery. Bariatric surgery is an effective tool and acts as preventive measurement in development of new obesity-related comorbidities (Buchwald et al. 2004; Cancello et al. 2005; Silberhumer et al. 2006). Bariatric surgery results in decreased healthcare utilization and lowers substantially direct healthcare costs. Bariatric surgery has partially evolved into new field, metabolic surgery, which does not focus primarily on weight loss, but on improvement and resolution of serious metabolic, obesity-related comorbidities, namely type 2 diabetes mellitus. It has been demonstrated that metabolic surgery leads in about 70–90 % of diabetic individuals to substantial improvement or complete remission of type 2 diabetes mellitus independently of weight loss.

Bariatric surgery in adults is an established and integral part of the comprehensive multidisciplinary management algorithm of morbidly obese patients.

17.1.3 Guidelines on Bariatric Surgery in Children and Adolescents: General Overview

On contrary with guidelines applicable to adult obese population, there's still lack of consensus on specific guidelines and algorithms for surgical treatment of morbidly obese children and adolescent. Of course, a "simple, nonsurgical solution," thus in the first instance decreasing energy intake and increasing physical activity, is appealing. Energy intake is undoubtedly a significant variable in predicting adiposity, its real role in genesis of true obesity, and its interaction with level of physical activity remains, however, unclear. Similar uncertainty about level of importance and impact on the overall obesity prevalence applies to physical activity and socioeconomic factors influencing obesity evolution.

Bariatric and/or metabolic surgery intervention remains rather controversial in adolescent and childhood patients. Published data on bariatric treatment results in adolescents is sparse. However, there's no alternative left in long-term effective treatment, especially in cases of massively obese adolescents. Therefore, bariatric surgery intervention in highly obese adolescents should be considered as an effective and safe treatment option. As this is indeed the case, all possible efforts should be made to standardize bariatiric treatment modalities and position bariatric surgery correctly among the other multidisciplinary approaches tackling obesity.

Several guidelines for treatment of severe obesity in adolescents were published recently. When reviewing these guidelines, different recommendations in regard to approach, indications, and other inclusion/exclusion criteria to surgical treatment of adolescents obesity can be noticed. Published guidelines are either specifically

referring to surgical treatment of childhood and adolescents obesity, or adolescent obesity guidelines are integral part of the general guidelines for adulthood obesity treatment.

In 2006 guidelines on surgical treatment of obese adolescents were published, such as the Canadian clinical practice guidelines on the management and prevention of obesity in adults and children (Lau et al. 2006) and the National Institute for Health and Clinical Excellence. "Management of obesity in clinical settings (children): evidence statements and reviews" (National Institute for Health and Clinical Excellence 2006).

In 2007 and 2008 another set of guidelines was published on the same topic: the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guideline for clinical application of laparoscopic bariatric surgery (Society of American Gastrointestinal and Endoscopic Surgeons 2008), the Prevention and treatment of pediatric obesity: an Endocrine society clinical practice guideline based on expert opinion (August et al. 2008), the Inter-disciplinary European guidelines on surgery of severe obesity (Fried et al. 2007a), and the Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report (Barlow 2007).

In 2009 and 2010, further guidelines were published, such as Recommendations for Bariatric Surgery in Adolescents in Australia and New Zealand (Australian and New Zealand Association of Paediatric Surgeons and the Obesity Surgery Society of Australia and New Zealand and the Paediatrics & Child Health Division of The Royal Australasian College of Physicians 2010), the IPEG guidelines for surgical treatment of extremely obese adolescents (International Pediatric Endosurgery Group (IPEG) 2009), Scottish Intercollegiate Guidelines Network. 115—management of obesity (Scottish Intercollegiate Guidelines Network 2010), and Bariatric Surgery for Obesity (Dent et al. 2010). An excellent general review of guidelines for surgical treatment of obesity in adolescents, the Guideline review: bariatric surgery in youth (Aikenhead et al. 2011), was published in 2011.

17.1.4 Guidelines Specifics on Age, BMI, and Other Criteria

There is no general consensus throughout the published guidelines on inclusion and exclusion criteria. However elementary overlapping consensus can be found throughout the guidelines. To draw the entire picture correctly, it has to be mentioned that some of the guidelines for bariatric treatment of adolescents do not recommend bariatric surgery in children and adolescents at all, or state that such treatment option should be used only exceptionally, in highly selectively indicated patients and in very specialized units.

However, most of the guidelines recommend and state conditions under which bariatric surgery may be performed in adolescents. Among the most discussed criteria is the age and developmental stage, weight/BMI, previous attempts to lose weight, multidisciplinary team experience, including surgical and support

teams, and others. Standardization of postoperative follow-up and treatment protocols is emphasized as well.

Age and developmental stage: actual chronological age is not considered as relevant inclusion criterion. Most of the guidelines rather refer to developmental stage such as completed or nearly completed developmental and skeletal maturity, final or near to final adult height, and/or Tanner stages 3–5.

Weight/BMI: although it is widely acknowledged that weight/BMI is far from being ideal criterion especially in childhood and adolescents, most of the guidelines use similar BMI borderlines as for adults. Thus BMI > 35 kg/m^2 with presence of serious comorbidities (such as type 2 diabetes, hypertension, benign intracranial hypertension, obstructive sleep apnea, NASH, etc.) or BMI > 40 even without presence of serious comorbidities is referred to as eligibility criterion for bariatric surgery.

Previous attempts to lose weight: most of the guidelines stress that such attempts (ideally under medical supervision and of at least 6 months of duration) are mandatory before considering any bariatric treatment.

17.1.5 Bariatric Procedures Available and Follow-Up Surveillance

Similar to adult bariatric treatment, there's no consensus on specific, ideal "golden standard" surgical procedure for adolescents. Specific care has to be taken of genetic syndromes, such as Prader–Willi syndrome. Only after extremely detailed and careful consideration of an expert medical, pediatric, and surgical team, bariatric surgery may be considered in these patients (Fried et al. 2007b, 2008). Currently, there are several surgical techniques (types of operations) to choose from.

The most common are:

Food limitation (restrictive) operations, such as adjustable gastric banding or sleeve gastrectomy

Operations limiting absorption of nutrients and energy, such as biliopancreatic diversion (BPD/Scopinaro's procedure)

Operations combining both of the above principles, however, in different proportions, such as Biliopancreatic diversion with duodenal switch (BPD-DS), or different modifications of gastric bypass.

The pace of continuous increase in prevalence of morbid obesity in children and adolescents with obesity-related comorbidities warrants in young age groups primarily low-risk operations, such as adjustable gastric banding or other low risk procedures (Silberhumer and Miller 2006; Garcia et al. 2003; Widhalm et al. 2004; Chapman et al. 2004; Maggard et al. 2005; Stanford et al. 2003).

However, in certain genetic syndromes (i.e., Prader–Willi) after careful consideration of an expert medical, pediatric, and surgical team, operations limiting

absorption of nutrients and energy, such as BPD, are considered to be the most appropriate (Fried et al. 2008).

Multidisciplinary approach and experience of the team which is involved in pre-operation indication process, the surgical treatment, and postoperative follow-up is essential. Standardized, lifelong follow-up; surveillance; and nutritional, behavioral, and overall support of the multidisciplinary team as well as patient's and/or their parents commitment are crucial in long-term success in treatment of obese adolescents.

As an important factor, surgical experience in care of adult bariatric patients, access to all-day-round emergency services, importance of experienced staff being present all the time were also highlighted in several guidelines.

17.1.6 Discussion

The surgical treatment of morbidly obese adolescents still remains a controversial topic, mainly due to concerns about performing such surgery in non-adult population and the so far limited experience in this field.

On the other hand long-term favorable treatment results achieved with bariatric surgery are well documented in large numbers of severely obese adults, and bariatric surgery as a part of the comprehensive multidisciplinary approach to morbid obesity is fully accepted by all medical specialties dealing with current obesity epidemics. Bariatric surgery in adults leads not only to substantial weight reduction, but significantly improves/resolves serious, obesity-related comorbidities.

Data from large series of patients show that, i.e., T2DM resolves in 60–80 % of diabetics.

Improvement and/or resolution can be seen in total of 80–92 % of diabetics (Buchwald et al. 2004; Dixon and O'Brien 2002).

Although there is only limited data available from bariatric surgery treatment in children and adolescents, the so far published outcome results are extremely encouraging.

All the bariatric procedures are of overall low potential risk, namely adjustable gastric banding being among the safest available.

Bariatric surgery allows the adolescents to lose substantial amount of excess weight (50–70 % of EWL); moreover in more than 2/3 of the patients their obesity-related comorbidities completely resolve, and in almost 1/3 at least substantially improve. This is an overall experience and remarkable improvement and resolution of comorbidities is reported throughout the literature for all bariatric operations in adolescents. In some series even better results of bariatric treatment are reported in adolescents than in adults. This may be influenced by the fact that obesity per se and obesity-related comorbidities (especially T2DM) are more likely to resolve in case they do are not present for a long period of time before the operation

(Sugerman et al. 2003; Barnett et al. 2005; Capella and Capella 2003; Breaux 1995; Schauer et al. 2003; Garcia and DeMaria 2006).

In conclusion, data published on bariatric surgery treatment results on obese adolescent population show that surgery is a safe and effective treatment option for morbid obesity.

Adolescent candidates for bariatric surgery should be selected very carefully through truly multidisciplinary approach involving at least pediatricians, psychologists, dieticians, bariatric surgeons, and patients' families. Bariatric surgery should be then ideally performed in obesity treatment centers experienced in dealing with adult and adolescent obese patients.

However more multicenter data on surgical treatment of obese adolescents as well as further specific guidelines on this topic are needed and awaited (Fried 2008).

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Chapter 18
Cardiovascular Risk in Childhood Obesity

Thomas Reinehr

Obesity in childhood is an increasing phenomenon (Livingstone 2000). Childhood obesity has a wide range of serious complications and increases the risk of early illness and death in later life (Freedman et al. 1999; Ebbeling et al. 2002). As in adulthood, obesity in childhood contributes to an increased prevalence of cardiovascular risk factors, such as hypertension, dyslipidaemia, and impaired glucose metabolism (Freedman et al. 1999; Ebbeling et al. 2002). It is discussed that the exposure to these cardiovascular risk factors in early life may induce changes in the arteries contributing to the development of atherosclerosis in adulthood (Atabek et al. 2007).

In adults detectable abnormalities in vascular function typically precede the development of vascular anatomical pathology (Koskinen et al. 2009; Halcox et al. 2009). Vascular dysfunction, including reduced endothelial function and arterial compliance and increased inflammatory markers, is detectable in obese and diabetic subjects prior to the appearance of anatomical abnormalities (Koskinen et al. 2009; Halcox et al. 2009). This has led to the postulated sequence of events whereby early changes in vascular risk factors such as obesity, hyperlipidaemia, hypertension, and impaired glycaemia promote initial endothelial dysfunction and stiffness of small vessels. Inflammation and continued presence of these risk factors lead subsequently to atherosclerotic development with altered vascular structure and increased stiffness of the large vessels (Duprez et al. 2005).

A measurement of these early cardiovascular changes, which is predictive for later atherosclerotic disease, would be ideal especially in childhood to describe the cardiovascular risk. Measuring the intima-media thickness (IMT) has been reported as a new non-invasive marker for these early cardiovascular changes, which is

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predictive for later CVD and strokes in adults (Davis et al. 2001; Hurwitz and Netterstrom 2001; Lorenz et al. 2007).

18.1 Determination of IMT

Measurement of IMT is performed using high-resolution ultrasonography, most often at the carotid artery (CCA), though peripheral sites have also been examined. Images typically are collected from the leading edge of the lumen–intima interface on the far wall of the CCA. Visualisation of IMT can be challenging because the vessel thickness is small (reported average values in normal and obese children and adults range from 0.34 to 0.80 mm) (Wunsch et al. 2007). New developments like Tissue Harmonic Imaging (THI), Speckle Reduction Imaging (SRI), and Real-time compound/Cross-Beam Imaging (CBI) and improvements of the hardware (e.g. matrix array transducer) have been developed to improve image quality (Wunsch et al. 2007). However, not all new techniques help to improve the quality of measurement. In a validation study of IMT measurement a standardised phantom was measured with different linear transducers (6–14 MHz) and techniques such as fundamental ultrasound, THI, SRI, CBI, and SRI (Wunsch et al. 2007). A U-formed device from high-grade steel was manufactured by a precision engineer with a thickness of exactly 0.3 mm (Wunsch et al. 2007). This device was covered by a medical condom. To avoid torsions this covered device was fixed in a massive frame made of aluminium. Thus the two opposing membranes of the condom were stretched absolutely parallel and horizontal to a distance of exactly 0.3 mm. This phantom was placed in a filled water container lined with polyurethane foam. A clamp at the water surface made an absolutely parallel position of the transducer possible to avoid lateral tilting of the transducer. The application of THI, especially when using lower frequencies (<10 MHz), caused extreme inaccuracies (Wunsch et al. 2007). The most exact measurements were collected using SRI and a 14 MHz linear matrix array transducer.

Apart from the technique standardised determination is necessary. The measurement of IMT should be performed at the CCA near the bifurcation at the far wall after a 10-min rest. The patients should be examined in the supine position with the head turned slightly to the side. An example of IMT measurement is shown in Fig. 18.1. Many studies have used the mean value of the measurements of IMT for statistical purposes. The strongest association among the different measurements of IMT between coronary risk factors in otherwise healthy individuals is reached by applying the maximum and not the mean value of IMT (Lorenz et al. 2007). This confirms the findings that atherosclerosis is not equally distributed in all the blood vessels, but that the extent of the thickening of the arterial wall differs in the various regions.

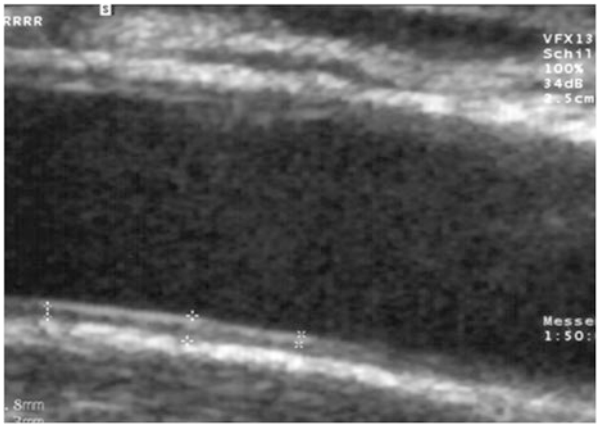

Fig. 18.1 IMT measurements at the far wall of the common carotid artery

18.2 Limitations of IMT Measurements

In most of the publications concerning IMT measurement the method of measurement is not even mentioned. If the method was mentioned, THI was most applied modality. Correct measurement of small structures is impossible using THI, because the post-pulse oscillation of the piezoelectric crystal is elongated when choosing this method. Therefore standardised protocols applying SRI or fundamental mode are necessary for reaching reproducible results (19).

Intra- and inter-operator variability can lower the significance of measurements. A skilled operator is required and probe placement must be optimised for each patient to locate stable images of regions of interest. The reproducibility of IMT measurements has been reported to be relative low even when conducted by an experienced group (Freedman et al. 2008). However, the use of automated contour identification methods for the analyses can reduce subjective image quantification, and is reported to reduce the variability while increasing the number of measurement points analysed (Cheng et al. 2002; Schmidt-Trucksass et al. 2001).

Although most reports presume that IMT is related to an initial atherosclerotic process (Lorenz et al. 2007) an increased IMT was also discussed to reflect a non-atherosclerotic adaptive response to changes in shear stress and tensile stress (Bots et al. 1997). Additionally, the ultrasound measurement of IMT does not allow to differentiate between intima thickening due to an atherosclerotic process or medial hypertrophy (smooth muscle growth) caused by the haemodynamic stimulation of a progressive increase in systolic blood pressure, pulse pressure, or arterial diameter over time (Davis et al. 2001; Lorenz et al. 2007; Bots et al. 1997). Finally, it has never been studied in childhood which IMT cut-points are predictive for atherosclerosis.

18.2.1 Age-Related Changes

Artery diameter increases with age in children as part of normal development, particularly in the lumen (Jourdan et al. 2005; Sass et al. 1998). Whether IMT changes with age is less clear. Some studies show an increase in carotid IMT with age in children (Jourdan et al. 2005; Hansen et al. 1995), while others show little or no change (Freedman et al. 2008; Sass et al. 1998). This is likely due to the very small changes that occur and the technical challenges of precise, reliable measurements. Interestingly, the changes of IMT in obesity and metabolic syndrome as described below have been reported already in a child aged 2 years (Weghuber et al. 2007) underlining the early age vascular changes occurred.

18.2.2 Risk Factors Associated to IMT in Childhood

Studies revealed associations between IMT, obesity, and many cardiovascular risk factors:

- *Hypertension:* One of the best recognised risk factor correlates with IMT in children is blood pressure. In a multivariate analysis of 96 obese boys and girls aged 9–13 years, systolic blood pressure contributed the most (15 %) to the variance in IMT (Reinehr et al. 2006). Further, increased IMT is often found in children with hypertension or borderline hypertension (Glowinska-Olszewska et al. 2007; Reinehr et al. 2006; Litwin et al. 2004; Sorof et al. 2003). Another study confirmed that daytime systolic blood pressure, measured with ambulatory monitoring, was positively correlated ($r = 0.57$) with carotid IMT (Lande et al. 2006).
- *Dyslipidaemia:* Studies in children and adolescents with familial hypercholesterolaemia and hypertriglyceridaemia demonstrated that cholesterol and triglyceride concentrations were predictive of carotid IMT (Lavrencic et al. 1996; Guardamagna et al. 2009; Noto et al. 2006; Rubba et al. 2001).
- *Metabolic syndrome:* In a study of young adults (mean age ~ 32 years) without diabetes carotid IMT increased progressively with the number of metabolic syndrome components present (Tzou et al. 2005). Consistent with other studies, elevated blood pressure was the strongest single predictor of IMT, but low HDL-cholesterol (<40 mg/dL) was also closely related. Fasting glucose, triglycerides, and waist circumference contributed progressively less to the variation in IMT (Tzou et al. 2005). Likewise, in overweight Latino children (mean age 11 years) who were followed over 3 years, consistent presence of metabolic syndrome at annual visits was associated with higher carotid IMT compared to those children without metabolic syndrome (Ventura et al. 2009). In comparison, in a study of 161 obese children, IMT was not significantly different in the subset of children with metabolic syndrome compared to those without (Mimoun et al. 2008). However, individual components of the metabolic syndrome and

their potential relationships to IMT were not analysed. Furthermore, multiple definitions of the MS have been proposed for adults and children agreeing on the essential components—glucose intolerance, central obesity, hypertension, and dyslipidaemia—but differing in detail (Reinehr et al. 2007). Of all these components, impaired glucose tolerance demonstrated the best predictive value for IMT values (Reinehr et al. 2008), even superior to all proposed definitions of the MS.

- *Diabetes:* In children with type 1 diabetes carotid IMT values were >10 % higher than age-matched peers with similar BMI, lipids, and blood pressure (Jarvisalo et al. 2002, 2004; Harrington et al. 2010; Heilman et al. 2009; Rabago et al. 2007; Schwab et al. 2007; Dalla et al. 2007; Short et al. 2009). The effect of type 2 diabetes on IMT in early life has been analysed only in a few studies (Short et al. 2009; Shah et al. 2009; Urbina et al. 2009). Urbina and colleagues showed that carotid IMT was higher in children and young adults (age range 10–24 years) with type 2 diabetes compared to lean or obese peers (Urbina et al. 2009). As might be expected for a group of children who developed type 2 diabetes at such a young age, the diabetic group in that study had several confounding risk factors compared to the lean or obese non-diabetic groups, including abnormalities in blood pressure, total cholesterol, triglycerides, glucose, and insulin, all of which might have contributed so these differences may contribute to the variation in IMT results observed. Nevertheless, modelling analysis showed that the predicted increase in IMT from the age of 10–24 years was negligible in lean participants, but accelerated by both obesity and type 2 diabetes.
- *Other cardiovascular risk factors:* Further markers of atherosclerosis such as the inflammation factor high sensitive C-reactive protein (hsCRP) have been shown to be a predictor of cardiovascular events in both healthy subjects and patients with coronary disease in prospective studies (Schulze et al. 2009; Ridker and Silvertown 2008). HsCRP was also significantly related to IMT (Reinehr et al. 2006). Furthermore, hyperandrogenaemia has also been reported to be associated with IMT in adolescents (de Sousa et al. 2009). This is of particular interest since hyperandrogenaemia is a classical feature of polycystic ovarian syndrome which is associated with obesity, metabolic syndrome, and insulin resistance.
- *Obesity:* In obese children, an increased IMT was reported in several studies (Reinehr et al. 2006; Short et al. 2009; Wunsch et al. 2005, 2006; Mittelman et al. 2010), while one study reported no statistically significant difference in the carotid IMT between severely obese children and lean control subjects (Short et al. 2009). The lack of difference in IMT in this study may be due to the relatively younger developmental age of the participants compared to other investigations. Interestingly, the IMT of obese children was significantly related to systolic blood pressure, glucose, and hsCRP (Reinehr et al. 2006; Short et al. 2009; Wunsch et al. 2005, 2006), suggesting rather a link between atherogenic changes and the cardiovascular risk factors hypertension, impaired

glucose metabolism, and chronic inflammation than a direct link between obesity per se and IMT.

18.2.3 Impact of Obesity and Cardiovascular Risk Factors in Children on IMT in Adults

Further support that childhood obesity and presence of risk factors negatively affect vascular health in adulthood has been provided by prospective studies that followed children for several decades. The Muscatine Study, which began data collection on 14,000 school children in the 1970s, showed that risk factors measured at the age of 8–11 years were predictive of IMT in a subset of 750 participants when those men and women reached the age of 33–42 years (Davis et al. 2001). Adult IMT was positively associated with childhood LDL-, HDL-cholesterol concentration, triglyceride, and blood pressure. A similar investigation over the same time period, the Bogalusa Heart Study, confirmed that elevated LDL-cholesterol and BMI in childhood were positive predictors of carotid IMT in adulthood (Berenson 2002; Freedman et al. 2008). A similar longitudinal study conducted in Finland has reached many of the same conclusions, and has recently reported that childhood levels of serum apolipoproteins B and A-I, measured at the age of 8–10 years, were significantly correlated with carotid IMT when measured in young adulthood (24–39 years) (Juonala et al. 2008). Furthermore, the Finnish group found that the apo B/apo A-I ratio was a better predictor of adult IMT than either LDL-C or LDL/HDL ratio. Perhaps the key message to emerge from these studies is that long-term obesity, present from childhood into adulthood, is most likely to be associated with elevated IMT.

18.3 Changes of IMT in Obese Children with Change of Lifestyle

The appropriate approach to reduce the obesity-related health risks is increasing physical activity and weight loss. A decrease of IMT has been reported in obese children who increased their physical activity (Farpour-Lambert et al. 2009; Meyer et al. 2006a). Two studies in obese children reported decreasing IMT in weight loss (Wunsch et al. 2006; Iannuzzi et al. 2009) demonstrating the reversibility of the early atherogenic changes. Therefore, intervention in obese children may prevent cardiovascular diseases in later life.

18.3.1 Further Methodological Approaches Assessing Vascular Function and Structure

Endothelial function is often measured with the non-invasive method of flow-mediated dilation (FMD). The most common method of assessing FMD is to measure the change in brachial arterial diameter in response to brief (5 min) arterial occlusion (Meyer et al. 2006b; Corretti et al. 2002). Flow occlusion is performed with a blood pressure cuff and Doppler ultrasound is used to image the artery diameter during and for up to 5 min after occlusion. Once the cuff is released the resumption of flow creates shear stress on the vascular wall, which stimulates nitric oxide production by the endothelial lining and in turn causes relaxation of vascular smooth muscle. The brachial artery typically dilates ~6–12 % in healthy people (Corretti et al. 2002). Elevated IMT values have been reported to be associated with lower brachial FMD in overweight children (Meyer et al. 2006b). Furthermore, the finding that a reduction in FMD was evident while a change in IMT was not detected supports the hypothesis that functional changes are likely to precede anatomic changes in vascular health (Short et al. 2009). However, although ultrasound has been the standard approach to measure FMD and associated changes in blood flow, this technique requires skilled operators and expensive instrumentation, and acquiring reproducible results can be challenging. For this reason, results may vary among research sites and application to clinical practice has been limited (Corretti et al. 2002).

Arterial compliance is the amount of arterial expansion and recoil that occurs with cardiac pulsation and relaxation, and is linked to both structural and functional properties of the artery (Arnett et al. 1994). There are several non-invasive methods available to measure arterial compliance, including diastolic pulse contour analysis (PCA), pulse wave velocity (PWV), and high-resolution ultrasound. Ultrasound approaches are used to assess arterial compliance as the change in lumen diameter from diastolic to systolic phases, typically at the carotid artery (Arnett et al. 1994). All of the methods used to measure compliance may vary with the site of measurement (central versus peripheral) and must be adjusted for pulse pressure. Some authors reported that pulse wave velocity but not intima-media thickness are changed in hypercholesterolaemic children suggesting that these alterations in arterial compliance occur before change of IMT (Riggio et al. 2010). Care must be taken to standardise measurements to control for several factors that affect the measurements including time of day, smoking, intake of food, caffeine or other stimulants, prior exercise, room temperature, menstrual cycle phase, and mental stress.

In summary, early vascular changes are already detectable in very young obese children by IMT measurements using standardised protocols. The increase of IMT is strongly related to cardiovascular risk factors summarised as the metabolic syndrome and other cardiovascular risk factors such as hsCRP as compared to obesity per se. Increase of IMT is reversible in weight loss and increased physical activity supporting the need of early intervention in childhood obesity.

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