

# Chapter 2

## Insulin Resistance in the Morbidly Obese Adolescent

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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- $\alpha$ , 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 adiposity (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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