Intraperitoneal Adipose Tissue: Associated Health Risks, Quantification by Advanced Imaging Methods and Future Directions in Children

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Abstract: The prevalence of obesity continues to grow at an alarming rate and currently there are no highly effective long-term treatments for obesity at the population level. Targeting childhood is a critical component of the strategy for fighting the obesity epidemic and there is an important need to understand the relationship among adipose tissue distribution, growth and obesity-related health risks. Growing evidence supports the idea that visceral adipose tissue (VAT) is related to insulin resistance, metabolic syndrome, cardiovascular disease, diabetes and other medical conditions through blood drainage, hormonal factors, inflammation, and adipocytokines. Recent studies suggest that VAT is not a homogenous depot. Intraperitoneal and extraperitoneal adipose tissues (IPAT & EPAT), the two subcomponents of VAT, have different venous blood drainage and may also differ in their associations with metabolic risk. The majority of previous studies have used imaging methods to measure the total amount of VAT. Few studies have established protocols for the analysis IPAT and EPAT and those that have are limited by their approximate nature and relatively large measurement error. To better understand the role of adipose tissue distribution in relation to the health consequences of obesity, accurate methods to separately measure IPAT and EPAT should be developed. Fortunately, children's characteristic VAT distribution permits easier differentiation between IPAT and EPAT than in adults. Future studies need to elaborate the role of regional VAT in growth and obesity with accurate quantification of IPAT and EPAT by advanced magnetic resonance imaging methods.

Keywords: Intraperitoneal adipose tissue, extraperitoneal adipose tissue, magnetic resonance imaging, growth, body composition.

INTRODUCTION

Obesity is becoming a global health risk and childhood obesity continues to increase at an alarming rate [1-4]. Visceral adipose tissue (VAT), though a small proportion of total adipose tissue, has been found to be closely related to health risks associated with obesity. Recent studies suggest that VAT is not a homogenous depot [5, 6]. Advanced imaging and surgery techniques have suggested that sub-depots of VAT, including intraperitoneal adipose tissue (IPAT) and extraperitoneal adipose tissue (EPAT), may have distinct metabolic activities [7-9]. IPAT, which consists of omental adipose tissue and mesenteric adipose tissue, is believed to be most strongly correlated with the health risks of obesity [6, 7, 9, 10].

Here we provide an overview of the relationship between health risks and IPAT based on a critical analysis of previously published results. We then examine existing imaging methods for measuring IPAT. Our report explores the importance of investigating IPAT in children and provides suggestions for future research. We believe that understanding the relationship between VAT and its growth in early childhood is an important component of the strategy for

IPAT AND RELATIONSHIP TO HEALTH RISKS

VAT, particularly the IPAT portion located in the mesenteric and omental areas, has been shown to be associated with health risks in animal studies, cross-sectional human studies and longitudinal human studies. In particular, VAT is associated with metabolic syndrome, cardiovascular disease and type 2 diabetes, mainly through insulin resistance [5, 11-17]. Additionally, VAT increases the risk of developing gastroesophageal reflux [17-18], cholesterol gallstones [19, 20], sleep apnea [21, 22], Alzheimer's disease [23, 24], stroke [25], cancer [26], and other chronic medical conditions.

The first theory to relate VAT to health risks was the portal theory, which is based on the observation that VAT directly drains into the liver via the portal vein. The high lipolytic activity of VAT and the expansion of this adipose depot in obese subjects results in direct exposure of liver cells to high concentrations of free fatty acids [9, 27]. Fatty acids influence liver production of glucose and triglycerides and the clearance of insulin by the liver [27]; this may account for the high frequency of metabolic complications associated with abdominal obesity [7-9]. However, it is the intraperitoneal subdepot of VAT that drains into the portal vein, whereas EPAT empties into the inferior vena cava [9,

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preventing childhood obesity and fighting the obesity epidemic.

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10]. Thus, distinguishing IPAT from EPAT is important for understanding the role of regional adipose tissue distribution in obesity related health risks.

In recent years, it has been recognized that adipose tissue is an endocrine organ [28, 29]. Adipocytokines such as adiponectin, leptin and resistin may mediate insulin resistance or modulate the likelihood that obesity results in the development of type 2 diabetes [30]. Adiponectin has anti-inflammatory and anti-atherogenic effects as well as multiple beneficial effects on metabolism. As opposed to proinflammatory adipokines, adiponectin levels are reduced in obese or diabetic individuals, particularly among patients with excess visceral adiposity [31-33]. Reduction of adiponectin is independently related to type 2 diabetes [30, 34]. Similarly, the expression of adiponectin receptor AdipoR1 is reduced in adipose tissue of obese subjects, with lower expression in omental adipocytes than in subcutaneous adipocytes [35]. The down-regulation of adiponectin receptors in adipose tissue of obese subjects appears to be reversible and 80% of the expression can be restored after significant weight loss [35]. Although the action of adiponectin in the liver and in skeletal muscle cells has been studied, the role of adiponectin in adipocytes needs to be clarified in future studies [35]. Resistin, another adipocytokine, impairs insulin action on hepatic glucose production and inhibits glucose uptake in skeletal muscle [36-38]. Resistin is positively associated with VAT accumulation and may partially explain the relationship between adipose tissue distribution and cardiometabolic risk factors [39].

The relationship between VAT and health risks can also be partially attributed to its secretion of inflammatory markers such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [32]. Additionally, obesity and VAT accumulation have been found to be the critical correlates of elevated plasma C-reactive protein (CRP) - another inflammatory marker – found in men with atherogenic dyslipidemia with the insulin resistance syndrome [40]. VAT also secretes markers of hemostasis and fibrinolysis [41, 42] and abdominal obesity is associated with increased plasma levels of fibrinogen, FVII and FVIII coagulant activities, as well as tissue plasminogen activator (TPA) antigen and its circulating inhibitor (PAI-1) [41, 43-45]. In addition, elevated serum vascular endothelial growth factor (VEGF), which is an important angiogenic factor implicated in normal and pathological vessel formation, is associated with VAT accumulation in human obese subjects [46].

In recent years, adipose tissue biopsies from human subjects undergoing surgery has made it possible to study the metabolic activity and its regulation in omental and mesenteric adipose tissue. Several adipokines are oversecreted by omental adipose tissue in obese subjects and it is believed that these adipokines may link obesity to cardiovascular or metabolic comorbidities [47]. Not only stromal-vascular cells such as macrophages and endothelial cells, but also adipocytes in adipose tissue are active in stimulating inflammation [47-49]. Hypertrophic adipocytes have recently been shown to shift their immune balance toward the production of proinflammatory molecules, causing dysregulated adipokine expression and secretion [47, 50, 51]. It has also been found that TNF-α expression is higher in omental adipose tissue than in subcutaneous adipose tissue (SAT), which could contribute to cardiovascular risk in centrally obese subjects [52]. In a study comparing omental adipose tissue, SAT, and liver biopsies, twice as many macrophages were found in omental adipose tissue than in subcutaneous adipose tissue [53]. Omental adipose tissue macrophage infiltration was correlated with insulin sensitivity, triglycerides, aspartate aminotransferase (AST), and γ-glutamyl transpeptidase. These results suggest that macrophages in omental adipose tissue participate in cellular mechanisms favoring hepatic fibroinflammatory lesions in obese patients [53].

One recent study sampled omental, mesenteric and subcutaneous adipose tissue in diabetic subjects [6]. This study showed that mesenteric adipose tissue in obese diabetic subjects has a high rate of basal lipolysis and impaired isoproterenol stimulated lipolysis. The PPAR-y gene expressions in the mesenteric, but not omental or subcutaneous adipose tissue, were up regulated. The 11β-HSD1 and FAT/CD36 gene expressions were higher in mesenteric adipose tissue than in subcutaneous and omental adipose tissues. These findings suggest that the alterations of these genes in mesenteric adipose tissue may play a critical role in insulin resistance in type 2 diabetes and metabolic syndrome [6].

A few studies have investigated the health benefits of omental adipose tissue removal. Omentectomy combined with adjustable gastric banding in severely obese adults (BMI >35 kg/m²) improved oral glucose tolerance, insulin sensitivity, and fasting plasma glucose and insulin 2-3times more than adjustable gastric banding alone [27]. The omentectomy group tended to lose more weight than the control group who underwent adjustable gastric banding alone (mean \pm SD, 36 \pm 14 kg vs. 27 \pm 17 kg, p = 0.07). As the sample size in this study was relatively small, larger scale studies are needed to clarify whether the health benefits of omentectomy are independent of weight loss [27]. A surgical protocol titled 'digestive adaptation with intestinal reserve' (DAIR) consisting of omentectomy, vertical gastrectomy and reduction of the small intestine, improved neuroendocrine profile and resolved diabetes [54]. The removal of the ometum reduces a major component of IPAT, which is believed to contribute to the beneficial effects of DAIR including decreasing a source of IL-6, IL-8, TNF-α, and resistin, as well as reducing insulin resistance in the liver [54]. However, the exact mechanism involved, other than weight loss, is not fully understood [55]. The lack of a control group in Santoro et al.'s study does not allow an accurate evaluation of the effects of omentectomy independent of vertical gastrectomy and reduction of the small intestine.

Surgical procedures have been used in animal studies in order to evaluate the effects of removing VAT on health risks. Omentectomy has been shown to increase insulin sensitivity in dogs [56]. Alternatively, rodent studies have shown that removal of EPAT can have beneficial health effects. It has been shown that removal of EPAT (i.e., perinephric and epididymal adipose tissue) prevents insulin resistance and glucose intolerance of aging in F344/Brown Norway and Zucker Diabetic Fatty rats [57], suggesting a potential causal relationship between VAT and insulin resistance. Similarly, Barzilai et al.'s study showed that removal of EPAT in moderately obese Sprague-Dawley rats

improves hepatic insulin sensitivity [58]. While the original rationale for VAT's relation to health risks is based on the portal theory [8, 9], the adipose tissue depot removed in this study is not drained by the portal vein. Instead, the perinephric and epididymal adipose tissue are drained by the vena cava. Therefore, these animal studies suggest that there may be additional mechanisms involved in the detrimental effects of VAT other than portal drainage. There is evidence that a series of genes, which might be implicated in the insulin-stimulated glucose transporter 4 translocation, are differentially expressed in the epididymal adipose tissue of rats rendered obese by a high fat diet [59]. Barzilai et al.'s study reported that the removal of EPAT did not cause significant reduction of total fat amount or total weight compared to the control group [57, 58]. Due to this fact, there is not enough evidence that the improvement of insulin sensitivity with removal of EPAT is mediated via weight loss. On the other hand, the findings in rodents may not necessarily be reproducible in humans. Future studies need to clarify the biological or pathological difference between IPAT and EPAT in humans as well as their role in obesity and associated health risks.

IPAT MEASUREMENT

Methods of direct measurement of VAT such as magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound, have been applied to both animals and humans. MRI and CT enable the visualization and quantification of adipose tissue mass in different compartments [9]. The choice between the MRI and CT is usually based on cost and availability of scanners as well as accuracy and reliability of image analysis. CT generates relatively consistent tissue attenuation values among images, thus the quantification of adipose tissue for CT is easier to implement than that of MRI. To minimize radiation dose, CT has mostly been used as a single-slice method in studying abdominal AT Distribution. On the other hand, MRI has several advantages over CT including its lack of radiation exposure and superior imaging of soft tissue. Furthermore, the lack of radiation with MRI allows for the determination of the total volume of adipose tissue compartments, which requires a longer scanning time.

In a study that compared the MRI measurement of three human cadavers to the direct measurement of adipose tissue mass after dissection of the cadavers, MRI was found to be an accurate and precise technique for the evaluation of VAT mass as well as the assessment of IPAT and EPAT [9].

Despite the high accuracy in measuring regional adipose tissue, the application of whole body MRI is limited by cost in most studies. A single cross sectional slice at specific anatomic locations is often used as a compromise between cost and accuracy for measuring VAT [33, 60, 61]. In adults of a wide range of adiposity, it has previously been shown that total VAT volume can be accurately estimated using the single slice method (i.e., at the L3 vertebra or 5-10 cm above the L4-L5) [33, 61, 62]. Because large scale studies have not been used to determine the anatomic distribution of IPAT and EPAT in humans, it is unclear whether a single slice can accurately estimate IPAT or EPAT. Furthermore, the anatomic location at which a single slice can provide the best

estimate of IPAT and EPAT total volumes is also unknown. Therefore, contiguous or multi-slice cross-sectional imaging methods, rather than single slice imaging methods, are the best choice when studying IPAT and EPAT, especially at the initial research stage.

In terms of distinguishing IPAT from EPAT on MRI slices, different methodologies exist for the approximate differentiation [9, 63-71]. Many studies rely on anatomic locations in order to establish an arbitrary line that separates the two compartments. For example, in previous studies, a straight line was drawn across the anterior border of the vertebra and the psoas major muscle, then continued tangentially toward the inferior borders of the ascending and descending colons and extended to the abdominal wall [63, 65, 66]. In slices where the kidneys were visible, an oblique line was drawn from the anterior border of the aorta and inferior vena cava to the anterior border of the kidney extending to the abdominal wall [63, 65-66]. IPAT was defined as the adipose tissue located anterior to the line drawn [63, 65-66]. However, it has been shown that this arbitrary method of quantifying IPAT and EPAT has an error of 3.8 to 49.4% when validated by high resolution MRI with the peritoneum visible [72] (Fig. 1).

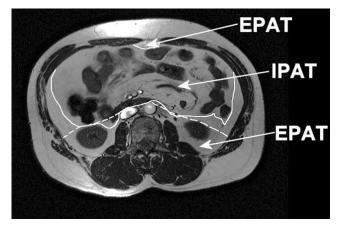


Fig. (1). The dashed line represents approximate separation of intraperitoneal adipose tissue (IPAT) and extraperitoneal adipose tissue (EPAT) as previously reported and the solid line represents visible separation of IPAT and EPAT [72].

The major difficulty for the separation of IPAT and EPAT in adults is that when VAT reaches a certain amount, IPAT and EPAT are adjacent to each other and common MRI protocols do not provide sufficient resolution for visualizing the fascia that separates the two compartments. The inconsistent reports on the relationship between IPAT and health risks in studies that use approximation methods could be attributed, at least partially, to the inaccurate measurement of the IPAT compartment. Although VAT can be detected in humans as early as infancy [73], there is a lack of studies on sub-dividing VAT into IPAT and EPAT in children. However, children have a much smaller VAT depot than adults [74] and omental adipose tissue is limited to the upper abdomen since the omentum is less developed in young children [75]. Therefore, the separation of IPAT and EPAT in children is more likely to be delineated by organs, even in children with a relatively large amount of VAT (Fig. 2). The Visible Human Project of the National Library of Medicine includes 1 mm thick consecutive high-resolution

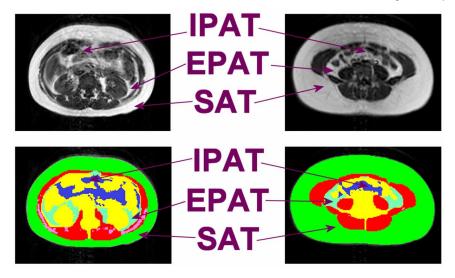


Fig. (2). The image clearly shows that intraperitoneal adipose tissue (IPAT) and extraperitoneal adipose tissue (EPAT) are separated by organs and muscles in a 14 year old girl with a relatively large amount of VAT volume (i.e. 1.6 L with 0.8 L or IPAT and 0.8 L of EPAT) comparing to an average of 0.6 L in girls [74].

axial photographs of a middle aged man and woman [76]. This digital image database allows 3-dimensional reconstruction of IPAT and EPAT as well as their sub-components. The analyst can gain detailed anatomic knowledge at different anatomic locations. Although variation exists among individuals, the continuation of IPAT and EPAT depots in consecutive images can serve as valuable references for segmenting IPAT and EPAT components. Even if arbitrary separation is still necessary in a small percentage of subjects at certain anatomic locations, the overall accuracy in quantifying IPAT and EPAT in children should still be much higher than that of adults.

Due to the limited availability of MRI and radiation of CT, indirect measurements of VAT such as ultrasound, Dual-energy X-ray-absorptiometry (DXA), and anthropometry are sometimes adopted for certain studies. However, DXA cannot separate SAT from VAT. Ultrasound has been used to measure the thickness of VAT, defined as the distance between the recto-abdominis muscle and the aorta [77] or the vertebral bodies [78]. Both the semi-quantitative non-volumetric nature of ultrasound and the inter-technician variability limit the application of ultrasound methods in measuring VAT. Waist circumference measurements reflect both SAT and VAT compartments as well as lean tissue in the abdomen. Although waist circumference is a good surrogate for VAT in large scale epidemiological studies [79-80], it does not provide an accurate estimate of VAT in studies of small sample size.

IMPORTANCE OF INVESTIGATING **CHILDREN**

Due to the lack of a long term weight loss or maintenance strategy that is easy to implement in adults [81, 82], preventing childhood obesity is an important strategy for fighting the obesity epidemic. However, existing information is fragmentary, leaving important gaps in our understanding of the relationship between adipose tissue distribution in the early years of life and obesity related morbidities later in adulthood.

Obesity in childhood is not only related to childhood health risks [83] such as metabolic syndrome [84] and insulin resistance [85], but also to adult obesity [86, 87] and associated morbidity and mortality [88, 89]. As growing evidence suggests that VAT conveys higher health risk than SAT, it is important to accurately quantify VAT and its subdepots in order to examine whether a connection exists between risk factors present early in life and the incidence of obesity in adulthood. Accurate measurement of the subcomponents of VAT in children is also important for phenotyping, which is a requisite for gene discovery, the evaluation of pharmacological effects in vivo, and the association of subject characteristics to health status and outcome.

Although the relationship between VAT and obesity related health risks has been relatively well established in adults [63, 66, 90-96], the role of VAT in the health risks for children remains controversial with inconsistent findings in previous studies [97-107]. A relationship between VAT and insulin sensitivity has been observed in obese adolescents [99, 103] but not in nonobese adolescents, young children [99, 104] or children with a relatively wide range of adiposity [100]. In a sample of prepubertal children ranging from lean to overweight, VAT was found to bear health risks similar to that of total body fat in a cross-sectional sample during the early recruitment period [100]. However, when the study sample reached a larger size, total body fat appeared to have the predominant effect on fasting insulin levels [100]. The longitudinal follow up of this sample showed that abdominal SAT may be more predictive of the rate of fasting insulin change than VAT [97, 101]. It has been suggested that the associations between VAT and health risks develop with age, sexual maturation, or establishment of disease [97].

Most investigations of VAT in children were based on a single image slice or a few aggregated slices near the L4-L5 level, which has proven not to be the best location for representing VAT volume in adults and children [33, 61, 62, 74]. Children have much smaller amounts of VAT than adults and thus a single slice at the L4-L5 level may be even less adequate to quantify VAT in children. Furthermore, while subcomponents of VAT (i.e., omental and mesenteric adipose tissue) may be closely related to health risks in adults, adolescents, and animals [8, 27, 108], there are no reports on the relationship between health risks and subcomponents of VAT in young children.

Using CT and MRI methods, it has been found that African American children have less VAT than Caucasian children [97, 104], but are more insulin resistant than their Caucasian counterparts after adjustment of total fat [97]. These observations confirm that ethnic differences in VAT amount exist in childhood. Interestingly, sex differences in VAT were not observed in childhood [74], even though sex differences in VAT have long been noticed in adulthood. There are no studies that examine whether ethnic or sex differences have an effect on IPAT or EPAT in children.

A unique feature of childhood is that almost all tissue compartments are growing. In a five year follow up study of children (ages 4.6 to 12.1 years at baseline), VAT exhibited significant growth [109]. However, Brambilla et al. found that during puberty there is a tendency for VAT to decrease in normal weight children and remain stable in obese children [110, 111]. Since puberty may have an independent effect on adipose tissue distribution [112, 113] and Brambilla et al.'s studies only included peri-pubertal children, it is possible that puberty contributes to the inconsistencies across these studies. Puberty may also influence the manner in which changes in adipose tissue distribution occur between lean and obese children. Some studies have suggested that adipose tissue deposition before puberty is more likely to be related to insulin resistance than adipose tissue deposition during or after puberty [114]. Further investigation is needed to clarify the relationship between growth, puberty, obesity and health risks. Using CT methods, Goran et al. found that the rate of change in VAT was similar among children remaining prepubertal compared to those who entered puberty during two years of follow up. However, VAT did not change significantly in the remaining group of four children who were more advanced in pubertal status during two years of follow up [115]. These results imply that not just puberty, but also pubertal stage, should be considered when studying growth and adipose tissue distribution.

As we have mentioned earlier, there are very few studies that examine the potential health benefits of omentectomy. To our knowledge there are no omentectomy studies in children. The DAIR surgical procedure, which includes omentectomy, has been performed on at least one 14 year old child, but there is a lack of clinical trials of adequate sample size in adolescents [116]. The role of omentum in confining inflammation should also be considered when evaluating the potential benefits of omentectomy.

FUTURE DIRECTIONS

With recent advances in MRI technology and the experience gained in VAT MRI analysis, higher resolution fast scanning sequences can make the development of IPAT analysis protocols possible. Recent advances in the Periodically Rotated Overlapping Parallel Lines with Enhanced Reconstruction (PROPELLER) data acquisition showed that

this technique reduces motion artifacts in pediatric brain scans [117-119] as well as breathing artifacts [120]. This technology advance, along with other fast imaging choices, provide potential solutions to the motion and breathing artifacts that have been considered problematic for pediatric MRI acquisition [121].

Future studies using advanced MRI protocols are needed to clarify the relationships between VAT partitioning, growth, puberty and obesity related health risks across different stages of childhood. Whether there are metabolic differences among the sub-depots of IPAT or EPAT may also be investigated in future studies. Clinical trials in children and adolescents are also needed to evaluate whether there are additional health benefits in regimes that target VAT or IPAT loss compared to overall weight reduction.

CONCLUSION

More knowledge about adipose tissue distribution and health risks in children is needed as part of our effort to understand and manage obese patients. Children's VAT partitioning is different from that of adults. Advances in MRI have made it possible for future studies to investigate subdepots of VAT including IPAT and EPAT. Although adipose tissue sampling in the omental and mesenteric adipose tissue compartments has greatly improved our understanding of the mechanisms at the cellular and molecular levels, biopsy of these adipose tissue depots is likely to be limited to morbidly obese subjects who undergo bariatric surgery. Imaging methods will need to fill in gaps when studying IPAT and its sub-depots in non-obese subjects or subjects in the very early stages of obesity. Accurate measurement of the sub-depots of VAT in children is important for phenotyping, which is a requisite for gene discovery and the evaluation of childhood obesity intervention methods. It is important to understand the early development of IPAT and its relationship to growth in order to construct childhood obesity prevention strategies. Future studies are also needed to establish whether weight loss interventions that target the reduction of VAT subdepots, such as omentectomy, are beneficial and practical in obese children.

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