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Obesity Diagnostic/Obesity Comorbidity

Use of MRI and CT for fat imaging in children and youth: what have we learned about obesity, fat distribution and metabolic disease risk?

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Summary

Childhood obesity is a matter of great concern for public health. Efforts have been made to understand its impact on health through advanced imaging techniques. An increasing number of studies focus on fat distribution and its associations with metabolic risk, in interaction with genetics, environment and ethnicity, in children. The present review is a qualitative synthesis of the existing literature on visceral and subcutaneous abdominal, intrahepatic and intramuscular fat. Our search revealed 80 original articles. Abdominal as well as ectopic fat depots are prevalent already in childhood and contribute to abnormal metabolic parameters, starting early in life. Visceral, hepatic and intramuscular fat seem to be interrelated but their patterns as well as their independent contribution on metabolic risk are not clear. Some ethnic-specific characteristics are also prevalent. These results encourage further research in childhood obesity by using imaging techniques such as magnetic resonance imaging and computed tomography. These imaging methods can provide a better understanding of fat distribution and its relationships with metabolic risk, compared to less detailed fat and obesity assessment. However, studies on bigger samples and with a prospective character are warranted.

Keywords: Children, fat distribution, imaging techniques, youth.

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Introduction

Obesity is associated with increased risk of metabolic diseases such as type 2 diabetes (T2D), cardiovascular disease, fatty liver disease and some forms of cancer. The persistence of risk factors for these outcomes from childhood and adolescence to young adulthood has been demonstrated (1), suggesting that the early prevention, identification and treatment are necessary.

The link between obesity and metabolic disease risk is driven by body fat distribution and ectopic fat deposition, but the only way to accurately visualize and quantify specific fat depots is state-of-the-art imaging techniques like computed tomography (CT) and magnetic resonance imaging (MRI). Recent advances in imaging techniques, especially in MRI, have made it possible to measure specific fat depots such as visceral abdominal fat (visceral adipose tissue [VAT]), subcutaneous abdominal fat (subcutaneous adipose tissue [SAT]) and ectopic fat depots including hepatic fat fraction (HFF), pancreatic fat fraction (PFF) and intramyocellular fat (IMCL fat) (2). The use of these methods in children yields new perspectives in studying the development of fat patterns during childhood as well as links to early metabolic risk (3).

The aim of the present review article is to review the existing evidence on the associations of total fat (TF) and specific fat depots, measured by MRI and CT, with obesity, along with the associated risk factors and comorbidities in children and youth.

Methods

We did an extensive search on MEDLINE using a combination of the following search terms (in titles and abstracts): (magnetic resonance imaging, computed tomography, imaging techniques) AND (body mass index, circumference, overweight, obesity, fat mass, total fat, abdominal fat (AF), visceral fat, subcutaneous fat, ectopic fat, hepatic fat, muscular fat) AND (children, adolescents, youth). In addition, we searched the bibliographies of relevant published articles. The present work is a descriptive review article.

Our research revealed 80 original articles expanding from 1992 to 2011.

Results

Abdominal and ectopic fat distribution during growth

Abdominal fat during growth

Subcutaneous adipose tissue and visceral adipose tissue. As advanced imaging techniques began to be used in children, an initial major question was if, and when, during childhood growth, does VAT accumulate. In one of the first reports using MRI in children, Fox *et al.* (4) studied 11-year-old children, selected to represent, by quintiles, the body mass index (BMI) range for their age. The authors described a wide variation of VAT, with amounts ranging from 6 to 58 cm^2 (mean = 17.8 +/– 10.0 cm^2) for boys and from 15 to 50 cm^2 (24.8 +/– 8.8 cm^2) for girls. The percentage of cross-sectional area taken up by VAT appeared to be less than in adults. However, approximately 1/3 of the children had a VAT/SAT ratio that has been associated with cardiovascular disease risk in adulthood. In a study conducted in healthy children (6.4 +/– 1.2 years; 24.8 +/– 5.4 kg), the mean SAT and VAT were 65.3 +/– 44.8 cm^2 and 8.3 +/– 5.8 cm^2, respectively (5). The VAT/SAT ratio was 0.15 +/– 0.08 whereas the VAT/TF ratio was 1.44 +/– 0.84, and VAT was associated with TF. In a study on early and late pubertal girls, VAT and SAT were derived from cross-sectional slices at the levels of the waist, hip and trochanter by MRI (6). VAT at the level of waist was 24.1 +/– 4.1 cm^2 and 25.7 +/– 4.1 cm^2 in early and late pubertal girls, respectively. Late pubertal girls had higher SAT at the level of trochanter compared to the early pubertal girls. Brambilla *et al.* compared obese and normal weight children (7) and showed that SAT and VAT were higher in obese children and SAT was predominant compared to VAT (353 +/– 94 cm^2 vs. 49 +/– 21 cm^2 for obese; 79 +/– 61 cm^2 vs. 22 +/– 11 cm^2 for controls). SAT and VAT were strongly related in lean but not in obese children. Similarly, Caprio *et al.* described that VAT and SAT were two- to threefold greater in obese girls (VAT: 137 +/– 10 cm^3 vs. 68 +/– 6 cm^3; SAT: 890 +/– 85 cm^3 vs. 303 +/– 45 cm^3) compared to non-obese girls (8). Asavama *et al.* tried to define thresholds for VAT in obese youth (9). A cut-off of 55 cm^2 based on cardiovascular disease risk factors was described for this population of Japanese children.

Some gender differences in VAT and SAT have also been described. Shen *et al.* suggested that VAT is not gender dependent for either pre-pubertal or pubertal children whereas SAT is gender dependent only for pubertal children (10). Benfield *et al.* observed that boys had lower levels of VAT and SAT than girls (11). VAT and SAT were higher in overweight and obese boys and girls when compared with normal weight children. Boys had higher VAT/SAT ratio than girls. This ratio decreased with obesity in boys but remained stable in girls, showing a patterning similar to adults (12).

Two studies have assessed VAT and SAT prospectively in children (13,14). In one 4-year study that followed obese, pre-pubertal children whose relative body weight did not change significantly during adolescence, VAT did not differ significantly for the three measurements whereas SAT increased significantly from the first to the third evaluation (13). In the other prospective study, two MRI measurements were performed during a 2-year period. In boys, VAT increased (VAT/SAT ratio from 0.31 to 0.39), whereas in girls, VAT decreased (VAT/SAT ratio from 0.39 to 0.35) (14).

A number of studies have also been performed in different ethnic groups. All studies in children conclude that African-Americans have lower VAT than Caucasians (15–18). In addition, Yanovski *et al.* described that African-Americans have less TF and SAT than Caucasians (15), whereas Goran *et al.* described an influence of ethnicity on VAT but not on SAT (16). In a prospective study over a 3- to 5-year period (18), growth of VAT was independent of growth of TF, whereas growth of SAT was dependent on TF and Caucasians showed a higher VAT compared to African-Americans. It has also been shown that Hispanic children are more obese, with higher central obesity than Caucasians (19,20). Liska *et al.* have described that Hispanics and Caucasians have similar VAT, and VAT was higher compared to African-Americans but SAT was similar for the three ethnic groups (21). In agreement, Hasson *et al.* (22) described more VAT in Hispanics but no differences as for SAT between them and African-Americans.

Summary: Prior studies demonstrate the accumulation of VAT very early in life at amounts generally related to overall adiposity. Nevertheless, the amounts of VAT and SAT cannot be compared in absolute terms with those of adults because of different body sizes and also to the greater physiological variations in TF during childhood and adolescence compared to adulthood. However, there are no established relationships as for VAT and SAT with age, maturation and gender. Discrepancies in the results obtained may be due to (i) small sample size; (ii) different designs (different degrees of maturation, only one gender vs. boys and girls, different degrees of obesity, MRI cross-sectional slices or volumes, etc.); and (iii) in most of them, the measurements of VAT and SAT were not coupled with TF which is highly related to different fat depots. Some ethnic-specific differences have been observed; Caucasians and Hispanics have more VAT compared to African–American youth.

Associations of abdominal fat depots with anthropometric indices. There is no consensus as to whether anthropometric measurements and indices such as waist circumference (WC), waist-to-hip ratio, BMI and skin-folds are interchangeable and, furthermore, whether they can predict or even replace more precise imaging methods (23).

BMI and WC are the most commonly used anthropometric indices for estimating total and regional fat in adults. A meta-analysis of the paediatric literature (24) showed that in children, WC was the best single predictor of VAT (64.8% of variance) whereas BMI was the best predictor of SAT (88.9% of variance). Benfield *et al.* (11) showed similar proportions of variance for VAT and SAT explained from WC and BMI, respectively. A study of 188 obese children (25) showed that those with high vs. low WC had correspondingly high vs. low VAT and SAT accumulation. However, the authors did not study the associations between BMI and VAT and SAT. In Hispanic children (26), an estimated 50% of VAT and 80% of SAT were explained by WC, but these predicting equations were only suitable for SAT.

As for skin-folds, Goran *et al.* (5) found that VAT was correlated with almost all skin-fold measures and with the trunk-to-extremity skin-fold ratio. Similarly, Fox *et al.* (14) proposed that truncal skin-fold sites were good indicators for VAT. However, more research is needed to confirm these findings, as another study by de Ridder *et al.* found that trunk-to-extremity skin-fold ratios did not predict VAT (6). Most of the studies in children show that waist-to-hip ratio is not a good indicator for predicting VAT (4–6), with the exception of one study on morbidly obese children (27).

Summary: It seems that WC and BMI are good predictors for VAT and SAT, respectively, in children, whereas waist-to-hip ratio is not. As for skin-fold thickness measurements and areas in the extremities, further studies are warranted. Nevertheless, it is of importance to mention that anthropometric measurements are strongly correlated and it is in general very hard to estimate their independent predictive value.

Ectopic fat during growth

A substantial portion of children accumulate fat in the liver (28) similar to adults. In a study by Radetti *et al.* in obese children (29), the degree of HFF (measured by MRI) was positively correlated with the hepatic enzymes but not with adiposity (not assessed by imaging techniques). In children with mild steatosis, normal alanine transaminase (ALT) levels were observed, whereas for severe steatosis, ALT was elevated, suggesting that abnormalities in hepatic enzymes occur in later stages of non-alcoholic fatty liver disease (30). Fishbein *et al.* observed that elevated ALT was associated with a higher HFF (31) and, in this study, HFF and VAT were associated. Again, in children, others have described associations of ALT with HFF (32,33).

Some interesting research has been done on fatty liver in African–American, Hispanic and Caucasian children. Liska *et al.* showed that for African–American, Caucasian and Hispanic children with similar weight and TF% (21), an excessive accumulation of fat in the liver (twofold higher than normal) was observed in both Hispanics (13%) and Caucasians (17.5%) but fat was undetectable in African-Americans. In agreement, Adam *et al.* have also demonstrated a higher HFF in Hispanics compared to African-Americans (34). In studies in multi-ethnic groups of obese youth, HFF has been associated with VAT even though an interaction with ethnicity is a question to be addressed (35–37). It has been recently suggested that a variant of the patatin-like phospholipase 3 gene (PNPLA3) is associated with fatty liver and this may explain a higher HFF in Hispanics compared to other ethnic groups (38–40).

In 2002, Sinha *et al.* demonstrated for the first time an early accumulation of fat in muscles, measured by magnetic resonance spectroscopy, in a paediatric population (41). In this study, IMCL fat was higher in obese compared to lean adolescents (0.85–3.76% and 0.46–1.22% of water resonance peak area, respectively). In the overall population, IMCL fat was associated with VAT but not with SAT. In addition, Cali *et al.* (42) have described that obese adolescents with fatty liver had also higher IMCL fat accumulation.

Some ethnic-specific characteristics seem to exist also for IMCL fat accumulation. Liska *et al.* showed that Hispanic children have the highest IMCL accumulation compared to African-Americans and Caucasians (21).

Recently, Lingvay *et al.* showed that lipid accumulation in pancreatic parenchyma is quantifiable and is associated with BMI and impaired glycaemia (43). To the best of our knowledge, only one study by Le *et al.* has measured PFF together with other fat depots (44). They showed that PFF was positively associated with VAT, HFF and free fatty acids (FFAs). In addition, Hispanic youth had higher PFF compared to African-Americans, but no comparisons were performed between Hispanic and Caucasian children.

Summary: Children accumulate fat in the liver, muscles and also in the pancreas. ALT seems to be the best circulating predictor for HFF. In addition, interrelations among HFF, IMCL fat and VAT have been described. There is also evidence on ethnic-specific characteristics. Hispanics have the highest IMCL fat accumulation compared to African-Americans and Caucasians, whereas HFF is very low in African-Americans compared to the other two ethnic groups. Hispanics have also higher PFF compared to African-Americans.

Lifestyle factors influencing abdominal and ectopic fat during growth

A number of observational studies and controlled trials have assessed the impact of diet and physical activity on specific fat depots measured by imaging methods.

Two cross-sectional, observational studies showed different results (45,46). In one of them (45), physical activity was associated with lower VAT but not with SAT, whereas in the other (46), energy intake but not physical activity was a predictor of VAT.

As for controlled trials, in a strength training (ST) intervention study in obese pre-pubertal girls (47), TF and SAT increased whereas VAT remained unchanged. This is surprising but it may be due to the effects of diet (children that exercise more, eat more and they subsequently accumulate more TF). In contrast, Owens *et al.* described a decrease in TF and SAT and a significantly less increase in VAT in the physical activity group compared to the control group in obese children (48). Gutin *et al.* studied three intervention groups: (i) biweekly lifestyle education (LSE); (ii) LSE + moderate-intensity physical training; and (iii) LSE + high-intensity physical training (49). In this study, they described a reduction in VAT and TF for both high- and moderate-intensity groups in agreement with others (50,51).

Davis *et al.* reviewed four randomized trials on Hispanics (52) with the following intervention programs: (i) ST; (ii) modified carbohydrate nutrition program (N); (iii) combination of N + ST; and (iv) N + combination of ST and aerobic exercise. They described that ST improved S_i in Hispanic boys, whereas for the other studies, glucose control for Hispanic boys and girls was improved. When aerobics, ST and N were combined, there was a reduction of all adiposity measures by ~3% in Hispanic girls. Moreover, participants who had decreased added sugar, had increased fibre intake and had increased parental attendance improved insulin action and decreased VAT. In agreement, a decrease in added sugar and an increase in fibre intake were associated with a decrease in VAT in an observational, prospective study in Hispanics (53), and with an improvement in S_i in a controlled clinical trial in Hispanics and African-Americans (54).

In a randomized controlled trial, involving (i) control group; (ii) nutrition (N) with emphasis on decrease in added sugar and increase in fibre intake; and (iii) ST + N, in obese African–American and Hispanic children, no effect on VAT, SAT or TF was observed (54).

Again in Hispanics, a controlled clinical trial involving aerobic exercise training in obese and lean children showed a decrease in insulin resistance (IR), VAT and HFF, and no changes for IMCL fat (55). These changes were observed only in the obese group. It was also suggested that HFF can be decreased by a combination of a balanced diet and physical activity in obese children (54,56).

Breastfeeding was also studied in a prospective, observational study in Hispanic children (57). The study showed no evidence for protective effects on TF or regional fat.

The associations of composition of diet in carbohydrates and fat with specific fat depots have also been studied in children. In a nutritional-intervention study by Treuth *et al.* where children consumed a high-fat, low-carbohydrate and low-fat, high-carbohydrate diet, TF and VAT were not associated with substrate utilization (58).

Interestingly, one study tried to examine the ethnic differences between African-Americans and Hispanics in the metabolic responses to a nutrition and physical activity intervention (54). In this controlled trial, African-Americans had higher SAT but lower VAT, HFF and S_i, compared to Hispanics, in agreement with previous findings (22). Both African–American and Hispanic children showed an improvement in their metabolic health, whereas no changes in VAT and SAT were observed and a decrease for HFF was evident, but it was not ethnic specific.

Finally, in Japanese obese children, after weight loss, the outpatient group did not decrease VAT/SAT, contrary to the in-patient group (59). However, because of the small sample size, it is not clear whether the differences between the two groups were random or truly associated to a stricter dietary intervention in the in-patient group.

Summary: Results are inconsistent as for the preferential effect of diet or physical activity on VAT and S_i. However, it is of particular interest that modifications in diet on added sugar and fibre intake can have a beneficial role in VAT reduction and S_i improvement. Physical activity seems to be beneficial also for VAT reduction.

Genetic factors influencing abdominal and ectopic fat during growth

Recently, it was demonstrated that the ancestral genetic background contributes to racial/ethnic differences in body composition above and beyond the effects of racial/ethnic classification and suggests a genetic contribution to TF, AF (measured by CT), lean mass and bone density (60).

It has also been proposed that there is a familial determinant for TF, VAT (61) as well as for IMCL fat (62) and fatty liver (63). Lee *et al.* showed that the telomere length was inversely associated with VAT in children (64). Pausova *et al.* (65) found an association between a functional variation of the androgen-receptor gene with VAT only in boys but not in girls.

FTO is a newly discovered gene associated with obesity in adults and children (66,67). A study on 485 adolescents (68) showed that a common variant of FTO was associated with higher TF and VAT. In contrast, in 1978 Caucasian and African–American youth (69), the FTO variant rs9939609 was not associated with VAT or SAT or IR and no interaction with ethnicity was observed.

Recently, the associations between the rs738409 variant of PNPLA3 and fatty liver in children were examined. Santoro *et al.* (38) described a frequency of the G allele of 0.324 in Caucasians, 0.183 in African-Americans, and 0.483 in Hispanics, and a higher prevalence of hepatic steatosis for the carriers of the G allele. However, the levels of hepatic and peripheral IR were similar for the G allele carriers compared to non-carriers. In agreement, in Hispanic youth, the prevalence of fatty liver was higher for the GG homozygotes compared to the other groups and there were no associations with VAT, SAT or insulin sensitivity (S_i) (39). In addition, it has been described that the GG carriers are more susceptible in developing HFF when dietary carbohydrate intake, specifically sugar, is high (40).

Abdominal fat and metabolic risk

Abdominal fat depots and lipid profile

In obese children, VAT has been associated positively with unfavourable lipid profiles (7,8,70,71) whereas SAT and femoral fat were associated negatively with low-density lipoprotein (LDL) (8). In a prospective study (13), obese, pre-pubertal children were followed over 4 years and MRI measurements were performed three times, and biochemical assays at baseline and at 4 years. In this study, VAT was positively associated with total cholesterol (TC) and LDL at the first measurement and positively associated with insulin and negatively associated with high-density lipoprotein (HDL) at the end of the study. These differences may be due to the cumulative exposure during 4 years to VAT. This study underlines the need for further prospective studies for assessing the long-term effect of VAT on cardiovascular risk in youth.

A number of studies have compared African-Americans and Caucasians but the effect of ethnicity on lipids and on their associations with VAT is still unclear. In most of the studies, VAT was positively associated with an unfavourable lipid profile. More specifically, associations were described with HDL (72–74), with triglycerides (TG) (73–76), with TC (73), LDL (73,74) and TC/HDL (73,74). However, Yanovski *et al.* (15) found no associations of VAT with serum lipids. As for the ethnic differences, some described higher levels of HDL and lower levels of TG for African-Americans compared to Caucasians (72,74). In contrast, Yanovski found no differences for serum lipids between African–American and Caucasian girls (15).

Abdominal fat depots and insulin action

VAT has been positively associated with higher fasting insulin levels in a number of studies in children (8,27,70,71).

In a study by Caprio *et al.* in obese girls, VAT was correlated with basal insulin secretion, stimulated insulin secretion and S_i (77). Liska *et al.* have also described inverse associations between VAT and S_i (21) whereas others described associations of SAT but not VAT with S_i (78). Bacha *et al.* observed no differences in VAT for normal glucose tolerance (NGT), impaired glucose tolerance (IGT) or T2D obese youth (79).

There seem to be some ethnic differences for glucose and insulin metabolism but the exact role of specific fat depots is unclear. In pre-pubertal girls (15), fasting and 2-h oral glucose tolerance test (OGTT) serum insulin levels were significantly correlated with SAT in African–American but not in Caucasian girls, suggesting racial differences even before the onset of puberty. No associations with VAT were found, maybe due to the small VAT depots in this population of normal weight children. In pre-pubertal children (80), African–American children had greater fasting insulin, incremental 30-min insulin and incremental area under the insulin curve. In regression analysis, fasting insulin was related to TF for both ethnic groups. Incremental 30-min insulin was associated with TF and VAT in Caucasian children only and area under the curve with SAT in African–American children only. The effect of ethnicity was not eliminated after adjustment on adiposity in the models. Other studies (81–84) have also described higher fasting insulin and lower S_i in African–American than in Caucasian children, suggesting that these racial differences may be due to other factors than fat distribution, amount of physical activity or cardiovascular fitness. Finally, Bacha *et al.* have shown that the dynamics of FFAs in the circulation are associated with insulin secretion and action and that African-Americans have lower FFA (compared to Caucasians), independent of fasting insulin and S_i (84). In agreement with the above, one additional study described more atherogenic profiles for Caucasian and more diabetogenic profiles for African-Americans (85).

Some studies have explored the associations of abdominal fat and insulin metabolism in Hispanics. Cruz *et al.* (86) demonstrated that in obese Hispanic children with a family history of T2D, VAT was positively associated with fasting insulin and acute insulin response (AIR – to assess insulin secretion) and negatively associated with S_i, independent of TF and SAT. VAT area was similar to that observed in African–American and Caucasian children (82). When Hispanic children with IGT and NGT were compared (87), there were no differences in body composition, S_i or AIR, whereas the disposition index (index of beta-cell function) was significantly lower in IGT by 16%. In a study by Goran *et al*., pre-diabetes was assessed over a 4-year period (88). Pre-diabetes was highly variable from year to year and children with persistent pre-diabetes had lower β-cell function due to a lower AIR and increasing VAT over time. Recently, Kelly *et al*. (89) observed prospectively in 253 overweight Latino children that compensatory changes in insulin secretion fail after Tanner stage 3 in both sexes, indicating beta-cell deterioration during this critical period of development; thus increasing the risk for T2D.

Some studies have also compared Hispanics and African-Americans, as for insulin and glucose metabolism. Hasson *et al*. observed that African–American children are more IR than Hispanic children and this difference was related to SAT (22). As a result of the decreased S_i, African-Americans had a compensatory higher AIR and enhanced β-cell function. The decreased glucose incremental area under the curve they described may reflect an overcompensation of the pancreas to maintain glucose tolerance. However, an acute hyperinsulinemia was not observed in response to the OGTT in African-Americans. It has been also suggested (34) that the individual fat depots in Hispanics are only related to fasting measures but not S_i; thus, the relative contribution of hepatic IR to overall IR in Hispanic girls is regulated differently compared with African–American girls.

Abdominal fat depots and metabolic syndrome

Recently, Syme *et al*. described associations between components of the metabolic syndrome (MS) and VAT in 324 adolescents (70). Subjects with high vs. low VAT had higher levels of fasting insulin, TG, homeostasis model assessment (HOMA) index and lower levels of HDL. In this study, VAT was not associated with fasting glucose or diastolic blood pressure (DBP) but there was an interaction for gender for the effect of VAT on systolic blood pressure (SBP). Similar associations with fasting insulin, TG, HOMA index and HDL were observed in obese Korean adolescents, and in addition, VAT was associated both with SBP and DBP (71). In addition, Druet *et al*. have demonstrated an association of VAT with the presence of MS in overweight children (90).

Toledo-Corral *et al*. examined the associations of carotid intima-media thickness (CIMT) with overall and abdominal adiposity in overweight Hispanic adolescents (91). Results indicated a high variability in the magnitude of CIMT change in this population and LDL cholesterol was the sole predictor for the 2-year CIMT progression. CIMT was not associated with VAT or SAT measured by MRI.

Summary: Signs of unfavourable lipid profile and disturbances of insulin and glucose metabolism can be already observed in childhood. However, more studies are needed to understand the role of abdominal and overall fat on these risk factors. Some interesting ethnic differences have also been described. African-Americans have lower TG and higher HDL than Caucasians, and lower S_i and higher fasting insulin compared to Caucasians and Hispanics. However, the interrelations of insulin, lipid metabolism and VAT in African-Americans, Hispanics and Caucasians are unclear yet. Discrepancies may be due, at least in part, to small sample sizes, different design methods, and also the measurement site of VAT and SAT (92,93).

Ectopic fat depots and metabolic risk

Some studies have been also conducted on the contribution of ectopic fat depots in on metabolic risk.

Burgert *et al*. observed positive associations of HFF with TG (37) whereas Oliveira *et al*. described differences in TG levels when children with and without HFF were compared (33). HFF was measured also in association with lipoproteins and their size (by nuclear magnetic resonance) (42). When subjects were categorized based on HFF, they all had normal LDL levels but differences were apparent for very low density lipoprotein (VLDL) and small dense LDL. In agreement, D'Adamo *et al*. described significant associations of HFF with large VLDL, regardless of ethnicity (35). HFF has also been positively associated with fasting insulin (32,34), with IR (32,33,36,42), and negatively with S_i (21,34,37). Associations of HFF with the prevalence of MS have also been described (36,37). Adam *et al*. have observed some ethnic-specific differences between African–American and Hispanic children as for the associations of HFF with insulin metabolism indices (34). In African-Americans, HFF was associated both with fasting insulin and S_i, whereas in Hispanics, there was a relationship only with fasting insulin, suggesting an interaction with ethnicity for the association of S_i with HFF.

IMCL fat has been also inversely related to S_i (21,41). Weiss *et al*. described associations of adiponectin with IMCL fat, suggesting interrelations between IMCL fat, adiponectin and S_i (94). When NGT and IGT children with similar degrees of obesity were compared by Weiss *et al*. (95), IGT children had higher IMCL fat (and also higher VAT and lower SAT), and IMCL fat was associated with IR. In agreement, Saukkonen *et al*. (96) showed that IGT obese children had increased IMCL fat.

As for the one existing study on PFF, no significant associations were found between PFF and markers of S_i or β-cell function (44).

Summary: HFF plays a pivotal role in lipid metabolism and is mainly involved in insulin metabolism in children. IMCL fat is related also with insulin metabolism. However, their independent contribution in insulin metabolism and overall metabolic risk is yet unclear.

Conclusion

In conclusion, use of MRI and CT technologies in paediatric studies has added greater understanding of how differences in fat pattern and metabolic risk emerge during life and vary across the population.

The accumulation of VAT starts early in life, although the effect of gender, age and maturation on VAT and SAT is yet to be clarified. WC and BMI are good predictors for VAT and SAT, respectively, although neither can differentiate one from the other, whereas the predictive value of skin-fold thickness measurements is not proven in children.

Besides the abdominal area, children accumulate fat in the liver, muscles and in the pancreas. Among hepatic enzymes, ALT seems to be the best predictor for HFF. HFF, IMCL and VAT seem to be closely related in children but their specific patterns are not known.

As for diet and physical activity, an increase in fibre and a decrease in added sugar consumption seem to have beneficial effects on VAT and S_i. Physical activity seems to be associated with a decrease in VAT.

Genetics may play a role in fat distribution and their association with metabolic risk. A genetic component has been proposed for IMCL fat and HFF.

The development of VAT and ectopic fat in the liver and muscle in childhood can drive the early development of IR and decreased insulin sensitivity. However, the interrelations of fatty liver, VAT and IMCL fat, as well as their independent contributions to insulin metabolism are still a matter of debate both in adults and in children.

Some racial differences have also been observed in children. Recently, it was suggested that the ancestral genetic background contributes to the racial differences for body composition. African–American children have less amount of VAT than Caucasians and Hispanics, better lipid profile but lower S_i and higher fasting insulin. In addition, Hispanic children have the highest IMCL fat and Hispanics and Caucasians have higher HFF compared to African-Americans. Hispanics have also higher PFF compared to African-Americans. Interestingly, the G allele of PNPLA3 is more frequent in Hispanics and it was very recently associated with HFF but not VAT or IR, suggesting a genetic component for HFF in Hispanics, independent of VAT accumulation.

Perspectives

Research in paediatric obesity, using MRI and CT, has offered new knowledge and promising results in the field. However, most of the studies are small in sample size, heterogeneous, in terms of pubertal status, age and gender, making it hard to be conclusive as for specific patterns of fat distribution and their associations with risk. Future studies on bigger, more homogenous paediatric populations, using these imaging techniques coupled with environmental parameters, can help establish patterns of fat related to gender, age groups and puberty. Moreover, following these populations through time would be of additional value for describing causal relationships between specific fat depots and metabolic risk.

Conflict of interest statement

No conflict of interest.

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