REVIEW ARTICLE

Intra-abdominal adipose tissue: growth, assessment and association with the development of metabolic alterations in children and adolescents

Tejido adiposo intra-abdominal: crecimiento, evaluación y su asociación con el desarrollo de problemas metabólicos en niños y adolescentes

Norma Ramos-Ibáñez

Abstract

The aim of the present review is to demonstrate the increase of intra-abdominal adipose tissue (IAAT) during growth and development and to describe methods to assess IAAT and the possible association with the development of metabolic alterations during childhood and adolescence. IAAT is characterized to have a high lipolytic activity and adipocytokine secretion that favor the development of insulin resistance, dyslipidemia and hypertension. IAAT naturally increases during growth in childhood; however, there is a wide variation in the amount of IAAT between children and adolescents. Magnetic resonance imaging and computerized axial tomography (CAT) are the most accurate methods to assess IAAT, but the cost of these methods limits their use at the population level. It is not recommended to use CAT to assess IAAT in healthy children due to radiation exposure. Currently, alternative methods have not been established to accurately assess this tissue. IAAT presents a positive association with blood pressure, insulin concentration, triglycerides and low-density lipoproteins (LDL), a decrease in the size of LDL particles, and a negative association with the concentrations of high-density lipoproteins (HDL).

Key words: intra-abdominal adipose tissue, adipocytokines, insulin resistance, dyslipidemia, hypertension.

Resumen

La presente revisión tiene como objetivo mostrar el incremento del tejido adiposo intra-abdominal (TAIA) durante la etapa de crecimiento, los métodos de medición del TAIA, y su posible asociación con el desarrollo de problemas metabólicos durante la niñez y adolescencia. El TAIA se caracteriza por tener alta actividad lipolítica y secreción de adipocinas que favorecen el desarrollo de resistencia a la insulina, dislipidemias e hipertensión arterial. El TAIA aumenta de manera natural durante la etapa de crecimiento; sin embargo, se observa una amplia variación en la cantidad de TAIA entre niños y jóvenes. La resonancia magnética y tomografía axial computarizada (TAC) son los métodos más exactos para medir el TAIA, pero el costo de estos métodos limita su uso a nivel poblacional. No es recomendable usar la TAC para medir el TAIA en niños sanos por la exposición a radiaciones. Hasta el momento no se han establecido métodos alternativos para medir con precisión este tejido. El TAIA presenta una asociación positiva con la presión arterial, las concentraciones de insulina, de triglicéridos y de lipoproteínas de baja densidad (LDL), y con la disminución del tamaño de las partículas de LDL; además de una asociación negativa con las concentraciones de lipoproteínas de alta densidad (HDL).

Palabras clave. Tejido adiposo intra-abdominal, adipocinas, resistencia a la insulina, dislipidemias, hipertensión arterial.

Departamento de Atención a la Salud, Universidad Autónoma Metropolitana Unidad Xochimilco, México, D.F., México
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Introduction

Obesity in children and adolescents is an ever-increasing health problem both in developed and developing countries.[1,2] Excess adipose tissue increases the risk of insulin resistance, dyslipidemia and arterial hypertension. Particularly, accumulation of intra-abdominal adipose tissue (IAAT) (tissue located around the gut into the abdominal cavity) has a greater influence on the development of metabolic complications (Figure 1).

IAAT is divided into two areas: intra- and extraperitoneal or retroperitoneal.[3] The intraperitoneal area is drained by the portal system and has a direct connection with the liver. The retroperitoneal area is located along the dorsal border of the intestines and the ventral surface of the kidneys and has no vascular connection to the liver.[4]

Metabolic characteristics of IAAT

IAAT is characterized by having a high concentration of adrenoreceptors â ($â_1$, $â_2$, $â_3$) that increase their sensitivity to catecholamines. Stimulation of these receptors promotes lipolysis, thereby causing the release of free fatty acids from the IAAT to the liver through the portal system. In contrast, IAAT presents lower concentrations of adrenoreceptors á and adenosine (which inhibit lipolysis) and decreased sensitivity to the anti-lipolytic effect of insulin.[4]

Figure 1. Intra-abdominal adipose tissue (IAAT) at the level of L4-L5 in a male adolescent with total body fat of 36%.

IAAT also presents receptors attenuated to androgen and estrogen. Testosterone inhibits the activity of the lipase lipoprotein and stimulates mobilization of triglycerides (TGs) in the IAAT, which leads to lower accumulation of this tissue in males.[5] Estrogen, like testosterone, has control on the lipase lipoprotein and reduces IAAT growth in females.[4] This effect of the sex hormones suggests that a decrease in their secretion may promote accumulation of IAAT once menopause occurs in women and andropause in men.

The increased fat in the IAAT is also related to the action of the hypothalamic-pituitary-adrenal axis. Stimulation of the hypothalamus produces corticotrophin-releasing hormone, which stimulates the secretion of cortisol in adrenal glands. Cortisol, in turn, favors the accumulation of TGs in the IAAT and inhibits their mobilization.[5] Re-esterification of TGs is ~50% greater in the IAAT than in abdominal subcutaneous adipose tissue, which seems to be regulated by acylation-stimulating protein.[4]

IAAT secretes a number of adipocytokines of peptide and non-peptide origin linked to metabolic alterations, such as tumor necrosis factor á (TNFá), activator inhibitor of plasminogen-1 (PAI-1), angiotensinogen, interleukin 6 (IL-6), leptin, resistin and acylation-stimulating protein (ASP) (Figure 2).

Studies in adults have shown that TNFá decreases the activity of insulin receptors, causing a resistance to this hormone.[6] This adipocytokine also increases the activity of the enzyme hormone-sensitive lipase, which leads to the release of fatty acids to the liver and a major production of low-density lipoproteins, thereby facilitating the development of atherosclerosis.[7] PAI-1 decreases the activity of the fibrinolytic system and increases the risk of vascular diseases.[8] Angiotensinogen has been linked with elevated arterial pressure, resulting from an increased activity of the rennin/angiotensin system.[6] IL-6, in turn, regulates the activity of lipase lipoprotein and increases the release of liver TGs.[9]

Leptin binds to the receptors in the hypothalamus that stimulate anorexigenic peptides such as neuropeptide Y, thus producing a decreased appetite and reduced food consumption. This adipocytokine also inhibits the process of lipogenesis and increases insulin sensitivity.[10] Leptin is secreted both intra-abdominally and in the subcutaneous area. However, ob-gene expression (produces and secretes leptin) is lower in the IAAT than in the subcutaneous adipose tissue.[11,12]

The adipocytokine-resistin appears to be linked to synthesis of hepatic glucose and lipid metabolism. It is strongly related to the development of insulin resistance and cardiovascular risk in adults.[13,14] ASP increases TG synthesis and in the IAAT leads to greater free fatty acid secretion to the liver compared with subcutaneous fat.[4,12]

Moreover, the largest accumulation of IAAT affects the secretion of adipocytokines called adiponectin. In children with a major accumulation of IAAT, we observe a low concentration of this adipocytokine as compared with those children with less fat accumulation in this area (6.4 ± 0.6 mg/L vs. 10.2 ± 0.8 mg/L; $p < 0.001$).[15] Adiponectin is a regulator of the fibrinolytic system, decreasing formation of hepatic glucose and increasing insulin sensitivity.[16]

Therefore, decrease of this adipocytokine generates insulin resistance, hypertension and alterations in the process of fibrinolysis in children and adults.[6,9,17] IL-6 and TNFá are also potent inhibitors of adiponectin secretion, which may be associated with increased insulin resistance.[16]

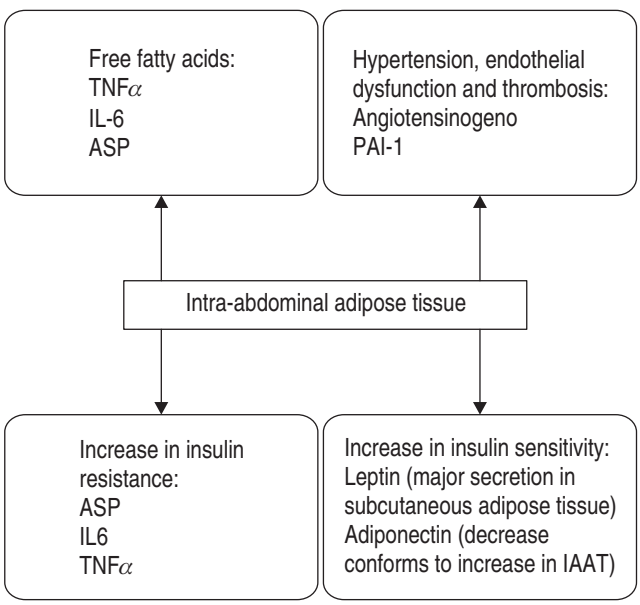

Figure 2. Metabolic effect of adipocytokines secreted by IAAT.

Direct measurement and estimation of IAAT

Computed axial tomography (CAT) and magnetic resonance imaging (MRI) are the most precise and accurate methods to measure IAAT. With these high-resolution imaging techniques we can identify the small deposits of IAAT. It has been observed that measurement of adiposity made with these methods has a high correlation ($r = 0.90$) with that obtained directly in cadavers.[18] CAT may have a precision error of 4% in the measurement of IAAT, whereas MRI measured IAAT with a CV of 1.4-4.2%.[20]

The IAAT measurement is reported in terms of area (cm^2) or volume (cm^3) of an anatomic point in the abdomen. The majority of studies report the measurement of IAAT at the level of lumbar vertebrae 4 and 5 (L4-L5) because it is considered to be the area where the largest quantity of IAAT is deposited in children.[21] Nevertheless, it is recommended that assessment of IAAT is done by multi-images from L1-L5 to increase measurement accuracy.[22] However, using this protocol increases the cost of the measurement. Using CAT to measure IAAT presents exposure to radiation and it is not recommended to expose healthy children to radiation because of the risk of developing cancer.[23] MRI is more appropriate to measure IAAT in children because with this technique we do not use ionizing radiation, instead magnetic fields and radiofrequency waves are used to produce images.[24]

CAT and MRI are techniques used to measure IAAT more frequently in samples of a few individu-

als, due to the high cost of the equipment (~1.5 million dollars), coupled with the cost per image. It is also necessary to have a trained technician for taking the images as well as a trained staff to interpret the value of the measurement of the IAAT with low error.

Intestinal peristalsis and respiration are variables that can affect image quality.[25] A low resolution of the image may lead to an under- or over-estimation of the measurement of IAAT. In children, it can become uncomfortable to remain inside the imaging equipment for the duration of the exam. It is not recommended in claustrophobic individuals.

Less costly and less invasive alternatives have been sought to be able to accurately estimate or predict IAAT. Different body composition assessment methods and anthropometric measurements such as plethysmography, dual X-ray densitometry, skinfold thickness, and waist circumference (WC) and hip circumference (HC) have been used in children and adolescents to estimate the area or volume of IAAT. These have been used in the U.S. and the U.K. As can be seen in Table 1, the techniques evaluated present a high coefficient of variation (20-67%) for estimating the area or volume of IAAT at these stages of life.[26,32] WC presents the highest coefficient of variation for the estimation of IAAT compared with laboratory methods, skinfold thickness and sagittal diameter along with the W/H index.

It is noteworthy that among the anthropometric measurements, WC has been promoted as a tool to establish distribution of adipose tissue in the central area and the risk of developing metabolic syndrome in adults.[33] In children and adolescents, its use as a means of prevention has begun to be recommended. In the Mexican-American population, WC values >75th percentile signaled special care for possible metabolic disorders and, even more so, if WC reaches the 90th percentile.[34] Nevertheless,

Table 1. Estimation of the measurement of IAAT in children and adolescents using alternative methods

Method used	Estimated measurement of IAAT	Population	r^2*	Coefficient of variation**
Dual-densitometry x-ray and abdominal skinfold[26]	L4-L5 level	113 American and African-American children (4-10 years of age, both genders)	0.85	28%
Sagittal diameter and W/H ratio[27]	L4-L5 level	76 American and African-American children (7-16 years of age, both genders)	0.63	24%
Subscapular skinfold and WC[28]	L4-L5 level	50 British children (11 years of age, both genders)	0.69	28%
Abdominal skinfold[29]	L4-L5 level	25 British males (13 years of age)	0.48	27%
Subscapular skinfold[29]	L4-L5 level	17 British females (13 years of age)	0.41	20%
Plethysmography[30]	Volume of 4 sites (L1-L2, L2-L3, L3-L4, L4-L5)	30 British males (13 years of age)	0.80	25%
WC[31]	Volume of 4 sites (L1-L2, L2-3, L3-L4, L4-L5)	22 British females (13 years of age)	0.77	34%
WC[32]	Volume of 5-20 abdominal sites	170 British adolescents (both genders, 12-13 years of age)	0.80-0.84	67%

*r^2, explains variance of IAAT, significant at p <0.01.
**Estimation of IAAT.
WC, waist circumference.

with this measurement we cannot establish if the value of WC is due to the accumulation of abdominal subcutaneous adipose tissue or due to the accumulation of IAAT. Some studies have shown that WC presents a high rate of error in the estimation of IAAT in Caucasian children.[31,32] In a review of the literature, in a total of 407 children and adolescents (7-16 years of age), both Caucasians and Hispanics, it was confirmed that WC presents a high CV (64.8%) in the estimation of the area (at L4 level) of IAAT. Neither ethnicity nor gender was a contributing variable to increase the estimate of IAAT.[35]

It was established that the method used to assess adipose tissue in the abdominal area (intra-abdominal and subcutaneous) should be accurate and precise with minimal measurement error.[36] Taking into account these criteria, the methods tested to date cannot be considered as exact and precise alternatives to replace the use of CAT and MRI in the assessment of IAAT in children and adolescents. However, some of the methods tested may be used to obtain a "rough" estimate of IAAT at a lower cost or implement anthropometric measurements that are more accessible for population studies.

Growth rate of IAAT

It is estimated that the growth rate of IAAT in children is 5.2 cm^2/year[1] as opposed to subcutaneous adipose tissue in the abdominal area, where the increase is 8 cm^2/year.[1,37] Thus far, we have not established the average value of IAAT level in relation to the age and gender of the population or the appropriate or healthy increase of IAAT, which may occur during childhood and adolescence. Some studies have reported the average value of IAAT found in the umbilical cord or L4-L5 in groups of children and adolescents (16-175 individuals) of both sexes, primarily of Caucasian background. Results obtained show wide variation in the increase of IAAT at different ages. At 6 years of age[38] IAAT presents a measurement of 8.3 cm^2 (range: 2-24 cm^2), whereas at the age of 7 years, the average value of the measurement is 31 cm^2 (range: 7-107 cm^2).[39] At the age of 11 years, a measurement of 17.8 cm^2 (range: 6-58 cm^2) was reported in boys and 24.8 cm^2 (range: 15-50 cm^2) in girls. In adolescent males of 13 years, IAAT increases to 30.1 cm^2 (range: 25-54 cm^2) and in adolescent females to 38.3 cm^2 (range: 26-59 cm^2).[29]

Reported values for IAAT for patients between 7 and 11 years old presupposed that there is a decrease in its accumulation. However, due to the lack of studies on measuring IAAT at these ages, we cannot actually say if a decrease occurs during the pre-pubertal stage or if the IAAT increases an average of 23 cm^2 in children between 6 and 7 years old. The average value of the IAAT measurement at 7 years of age was obtained from a population of 100 children (American and African-Americans) where the average first measurement was higher than in the latter measurement for both sexes (boys: 27 vs. 22 cm^2, girls: 54 vs. 28 cm^2).[39] This may show that the values of IAAT may vary by each ethnic group, independent of their age. Another possible explanation for this apparent reduction may be attributed to the equipment used in the studies (CAT vs. MRI) and anatomic point evaluated in the abdominal cavity (lumbar vs. umbilical level). In the study by Goran et al.[39] CAT was used, and the anatomic site was measured at the umbilical level in comparison to the study of 11-year-old males where the measurement of the IAAT was done with MRI at L4 level. Although CAT and MRI are accurate equipment, differences in image quality by the model used may be presented, thus affecting the accurate measurement of IAAT. Using the umbilical level as a reference to measure IAAT may not correspond to L4 level. As previously mentioned, the most frequently used anatomic site for measuring IAAT is between L4 and L5 vertebrae.

According to the previously mentioned data, the highest IAAT gain is seen during puberty. In males, IAAT increases 69% and in females the increase is 48%. In contrast, it has been observed that subcutaneous adipose tissue in the abdominal area increases in a lesser proportion in males (19%), whereas in females the increase is higher than in

IAAT (78%).[29] This shows the changes of distribution of adipose tissue that present during puberty. Although males show a lower value for IAAT at this age, the proportion of gain of this tissue is higher compared to females. In contrast, in females a larger gain in subcutaneous adipose tissue is observed.

As mentioned earlier, data reported on the measurement of IAAT have been principally collected in Caucasian populations. In Latino populations, only three studies have reported the measurement of this tissue. The first one evaluated the IAAT in 11-year-old children who were overweight ($n = 175$) where the measurement found was 47.3 cm^2 in males and 49.6 cm^2 in females (no limits were specified).[40] The second study was conducted in 12-year-old females with obesity ($n = 47$) and, in this group, it was found that the IAAT measurement was 86.3 cm^2 (range: 32-182 cm^2).[41] The third study was comprised of 8- to 13-year old children and shows that those who were breastfed in infancy from 0-6 months ($n = 33$) had a measurement of 44.1 cm^2. Those children who continued to be breastfed at 6-11 months ($n = 7$) had a measurement of 33.6 cm^2, and those children who were breastfed >1 year ($n = 24$) had a larger measurement (51.8 cm^2). Children who were not breastfed ($n = 53$) had an IAAT measurement of 45.8 cm^2.[42]

Given the characteristics of these studies, we cannot establish a comparison with results found in the Caucasian population. In the first two studies, IAAT was only evaluated in children with obesity[40,41] and, in the third study, measurement of IAAT was done in children who were not specifically assessed by chronological age as in previous studies.[42] Hence, we cannot establish whether Latin children present a greater IAAT value than Caucasians or if being overweight influences this value. According to the data presented in the third study, it is observed that children who were breastfed >1 year have high values of IAAT compared with other groups, although it was not shown if these differences were significant. Previous studies have examined the possible protective effect of breastfeeding against the development of obesity, but results are inconclusive.[43,44] Therefore, the question arises whether feeding during the first year of life or later influences IAAT accumulation in children.

It is not certain that the increase of abdominal subcutaneous adipose tissue or the increase of total fat mass influences the increase of IAAT in children and adolescents. There is a high correlation between IAAT and abdominal subcutaneous adipose tissue ($r = 0.85$, $p < 0.01$) with total fat mass ($r = 0.81$-0.85, $p < 0.01$) in children.[39,45] Nevertheless, after adjusting for total fat mass variable, there is no significant correlation between IAAT and abdominal subcutaneous adipose tissue.[39] In adolescents, it has also been seen that total fat mass and abdominal subcutaneous adipose tissue were highly correlated with the IAAT ($r = 0.77$, $r = 0.74$, $p < 0.001$, respectively).[46,47] However, in obese adolescents there is no significant relationship between IAAT with total fat mass and abdominal subcutaneous adipose tissue ($r = 0.12$, $p > 0.05$).[46] Despite the high correlation shown between IAAT and total fat mass, we cannot determine if changes in the latter have a direct impact on the increase of IAAT or if it is a result of other involved factors (such as endocrine or dietary).

IAAT and its association with metabolic problems

IAAT been considered as a possible trigger for metabolic disorders such as dyslipidemia, hyperinsulinemia and arterial hypertension. Three mechanisms have been proposed as causes for the development of these metabolic problems:[48-51]

1. Mechanical effect-excess of IAAT could add pressure to the liver and kidneys, thus altering normal function of these organs.
2. Secretion of adipocytokines-as mentioned earlier, IAAT releases TNFá that affects insulin receptor activity, thus favoring a possible resistance to it. IL-6 could lead to the development of hypertriglyceridemia due to their as-

sociation with TG secretion to the liver. Increase in arterial pressure could be caused by angiotensinogen, which stimulates activity of the rennin/angiotensin system, thereby producing sodium reabsorption in the kidneys. The risk of vascular problems may be associated with the secretion of PAI-1 by inhibiting the fibrinolytic system.

3. Liberation of fatty acids-IAAT is characterized by high lipolytic activity, resulting in increased release of free fatty acids to the liver. This process increases hepatic glucose production, thereby leading to glucose intolerance and hyperinsulinism.

It has been reported that an IAAT measurement of >40 cm^2 in children 7-10 years of age (American and African-American origin) is positively related to TG concentrations ($r = 0.42$-0.56, $p < 0.05$) and negatively ($r = -0.26$ to -0.40, $p < 0.01$) with concentrations of HDL.[52,53] In adolescents of 13-16 years of age (American and African-American), it is observed that IAAT presents a positive relationship ($r = 0.27$, $p < 0.05$) only with LDL concentrations.[54] These data suggest a possible association of IAAT with the development of dyslipidemia, principally due to alterations in the concentrations of TGs and lipoproteins. However, we have failed to establish whether this cause-and-effect relationship is latent in other ethnic groups of children and adolescents.

It has also been shown that IAAT may be related to the size of the LDL particles. In 13- to 16-year-old adolescents with an excess of IAAT, it appears that LDL particles are smaller in comparison with those in children with lower IAAT (250.5 vs. 258.7 Å, $p < 0.01$). It is believed that the smaller LDL particles have higher atherogenic potential.[55] Likewise, it has also been observed in 13- to 18-year-old males that an IAAT amount >358 g is associated with an increased thickening of arterial walls (200-400 μm) and macrophage density (200-600 mm^2),[56] conditions that may increase the risk of developing atherosclerosis.

Regarding the relationship of IAAT with insulin concentration, it has been estimated that the increase of 1 cm^2 per year of IAAT[1] increases fasting insulin by 5% in children.[57] On the other hand, it has been reported that the fasting insulin concentration is positively related ($r^2 = 0.56$, $p < 0.05$) with IAAT but presents no significant association ($p = 0.16$) with insulin sensitivity in children.[45] In adolescents there are no reports of any association between the IAAT and the insulin concentrations.[54]

Increase in systolic arterial pressure also presents a positive association with the IAAT ($r = 0.35$-0.73).[58] In children with a lower amount of IAAT, lower values of systolic and diastolic arterial pressure have been observed, compared with those that present a greater amount of adipose tissue in the abdominal cavity (systolic: 111.6 vs. 125 mmHg, $p = 0.006$; diastolic: 59.3 vs. 69.1 mmHg, $p = 0.006$).[59]

Conclusions

Adipose tissue, particularly the type found accumulated in the abdominal cavity, appears to be linked with the development of metabolic alterations. Because of the scarcity of studies that have reported the measurement of IAAT during the growth stage, we have not been able to establish in detail the amount of healthy or low IAAT associated with metabolic disorders in children and adolescents according to age and sex.

Although there is an association between total fat mass and IAAT, one cannot assert that the increase of the first influences the accumulation of adipose tissue in the abdominal cavity. It is possible that other endocrine and dietary factors have a more direct effect on the natural increase of IAAT during childhood and adolescence. It is necessary to conduct additional studies that more precisely define the changes presented in adipose cells of IAAT. Likewise, future studies are needed to establish whether adipocytes in this area present the same critical points of growth identified so far (last trimester of

gestation, first two years of life and puberty) or have a different growth.

MRI and CAT are methods regarded as the gold standard for assessing IAAT, but the high cost of the equipment and its technical characteristics limit its use at the basic level of care. Currently there is no alternative method that allows us to accurately assess IAAT in children and adolescents. Measuring WC has been proposed as a way to establish the risk of metabolic alterations, but we cannot consider this as an accurate measurement for estimating IAAT.

Undoubtedly, there is much that remains to be clarified on the role of IAAT in the development of metabolic alterations in childhood and adolescence. It is essential to conduct further studies in Mexican children and adolescents in order to understand with greater depth IAAT changes introduced during the growth phase, the possible factors related to the growth of this area and the relationship it has with the development dyslipidemia, insulin resistance and arterial hypertension.

Correspondence to: Norma Ramos Ibáñez
Departamento de Atención a la Salud
Universidad Autónoma Metropolitana-Xochimilco
México, D.F., México
E-mail: nramos@correo.xoc.uam.mx

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