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Ultrasound: Which role in body composition?

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ABSTRACT

Ultrasound is a non-invasive, fast, relatively inexpensive and available tool for estimating adiposity in clinical practice, and in several research settings. It does not expose patients to ionizing radiation risks, making the method ideal for the evaluation, and for follow-up studies. Several parameters and indexes based on adipose tissue thickness have been introduced and tested, and these have been correlated with clinical and laboratoristic parameters. Moreover, ultrasound can also be directed to the estimation of adipose tissue and intracellular fat indirectly, at cellular-molecular level: an opportunity for many radiologists who already and sometimes unconsciously perform "body composition" assessment when looking at the liver, at muscle as well as at other organs. However, standardized procedure and parameters are needing to improve accuracy and reproducibility. The purposes of this review are: 1) to provide a complete overview of the most used and shared measurements of adiposity; 2) to analyze technical conditions, accuracy, and clinical meaning of ultrasound in the study of body composition; 3) to provide some elements for the use of ultrasound in the evaluation of intra-cellular lipids accumulation, in two hot spots: liver and skeletal muscle.

1. Introduction

Obesity, defined as the pathologic accumulation of fat in the body, is one of the most common diseases all over the world, with its prevalence increasing worldwide in developed and developing countries; it affects all ages, and is highly involved in the development of metabolic disorders such as type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD). In 2010, overweight and obesity were estimated to cause 3.4 million deaths, 3.9% of years of life lost, and 3.8% of disability-adjusted life-years worldwide [1]; moreover, recent analyses estimate that the total economic cost of overweight and obesity amount to 90 billion dollars per year in the US and to 81 bilion euros per year in the EU. There is also increasing awareness of the influence of obesity in the pathogenesis of different disorders, apparently far from the field of metabolic or endocrinological diseases. As well, several diseases induce a metabolic change which is expressed by anomalous accumulation of fat in depots or organs. The terms "fat" and "adipose tissue" are often used as synonymous, but this is improper. According to the enlightening model proposed by Wang et al. [2] for body composition analysis, 5 levels of increasing complexity are described: atomic, molecular, cellular, tissue and total body level. Adipose tissue is a component of the tissue-organ body composition level, and in terms of weight is one of the most representative. This is a specialized loose connective tissue composed of adipocites (mainly), fibroblasts, collagen, capillars and extracellular fluid; it is the body's largest storage site for triglycerides (TG) and plays an important role as an endocrine organ in energy homeostasis. Historically, adipose tissue was considered as a passive reservoir for energy storage and a way to insulate and protect the body; however, more recently its critical role as body energy and homeostasis regulator, and as endocrinological active organ, has been recognized [3]. From an anatomical point of view, accumulating data support the idea that different sites and adipose tissues are organized to form a large organ with discrete anatomy, specific vascular and nerve supplies, complex cytology, and high physiological plasticity [4]; this is made up of several depots and can thus be considered a multi-depot organ [4]. On the other hand, at the molecular and cellular level, fat is usually found as lipids in the form of TG. Although fat is found primarily in adipose tissue, molecular fat also exists in other tis-

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sues, especially in pathological conditions such as hepatic steatosis and various forms of lipoidosis, in which fat accumulates inside the cells. Not to generate confusion, although improperly, the terms "fat" and "adipose tissue" will be considered synonymous, while the term "intracellular fat" will be used to describe lipids inside any kind of cells.

2. Body composition and "adiposity"

Vague, in the far 1947, was the first to notice [5] that the distribution of adipose tissue may influence the predisposition to metabolic diseases. Individuals with central obesity accumulate fat mainly in intra-abdominal and upper thoracic deposits; numerous epidemiological studies reported a close association between central obesity, insulin resistance (IR) and a cluster of different metabolic diseases. In contrast, individuals with peripheral obesity have a predominantly subcutaneous accumulation of fat in the femoral-gluteal region and seem to be less susceptible for metabolic complications, IR and dyslipidemia. These findings led to the hypothesis that accumulation of fat in specific locations may partially contribute to the association of adiposity with cardiometabolic risk. Among different adipose tissues, the one located inside the abdomen (and the thorax), around the abdominal organs, called "visceral" adipose tissue (VAT), has been recognized as the most dangerous, and several studies correlated this specific depot with several clinical and laboratoristic parameters of CVD and metabolic syndrome (MS). Multiple studies demonstrated that the visceral fat compartment is metabolically active, secreting a plethora of vasoactive substances as inflammatory markers and draining these substances directly into the portal circulation, which may contribute to its role in cardio-metabolic risks and manifestation [6]. Simultaneously, lipids in ectopic (non-adipose) tissues such as liver and skeletal muscle were associated with insulin resistance and adverse metabolic phenotypes, independently of total adiposity. Subcutaneous adipose tissue (SAT), on the other hand, plays a more uncertain and controversial role: many researchers see it as a passive reservoir for adipocites, with a neutral or protective role in the development of obesity-related disease [6,7], but some other studies questioned this role, finding an association between SAT and IR, especially at abdominal level [8]. For all these reasons, the evaluation and differential quantification of specific adipose tissue compartments in the body is of paramount importance, and several techniques have been proposed for this aim. Imaging has been propulsor in the clinical evaluation of body composition and this mainly happens on molecular and organ-tissue level. Computed tomography (CT) and magnetic resonance imaging (MRI) are usually considered the gold standard techniques, at organ-tissue level, but suffer from several limitations: high cost, low availability, elevated time consumption, and X-ray exposure for CT [9]. At the molecular level of body composition instead, other techniques have been proposed for estimating body fat percentage, with Dual-energy X-ray Absorptiometry (DXA) being the most widely used and validated [10]; however, DXA has a few limitations, for example it is not able to directly discriminate between visceral and subcutanous fat (2D technique). Ultrasonography is a non-invasive, fast and relatively available and inexpensive alternative for estimating adiposity in clinical practice [11]. It does not expose patients to ionizing radiation risks, making the method ideal for the evaluation of young people, and for follow-up studies or for large cohort of patients. Ultrasound is conventionally assigned to organ-tissue level, as it is able to measure different adipose tissue compartments, but this tool also allows an estimation of fat in terms of lipid content at both tissue and cellular-molecular level: indeed it can measure adipose tissues as thicknesses measurements, but it can also evaluate, in a few cases, intracellular fat content as change in tissue echogenicity.

3. Ultrasound imaging for body composition assessment

The first pioneering use of ultrasound for adiposity evaluation dates back to the 60′, focusing in particular on subcutaneous fat [12]. In 1990, Armellini et al. [13] were the first to describe a method for ultrasound evaluation of abdominal adiposity, and to compare this new assessment with CT. During the last three decades the interest in this technique for fat evaluation increased quickly and many ultrasonographic parameters and indexes have been proposed and tested. The aim of this review paper is to provide the reader with a complete overview of the most used and shared measurements of adiposity, and to analyze technical conditions, accuracy, and clinical meaning with their potential impact. We will also provide some elements for the use of ultrasound in the evaluation of intra-cellular lipids accumulation, in two hot spots: liver and skeletal muscle (Table 1 and Table 2).

3.1. Intra-abdominal fat

Intra-abdominal fat thickness (IAFT) is among the first measurements used in ultrasound evaluation of adiposity, and it is certainly one of the most important. Intra-abdominal fat is often used as synonymous for VAT, but this is misleading. VAT refers indeed to the fat depots surrounding the internal organs (viscera), and not to all intra-abdominal fat depots. Also from an anatomical point of view, there is no unanimous consensus on how ultrasonographic measures of IAFT have to be taken: in most articles, IAFT is measured from the posterior wall of the abdominal muscle (i.e. from linea alba) to the anterior wall of the aorta, as described by Armellini on his first work (Fig. 1) [13–17]. Anyway, some other authors measured IAFT from the abdominal muscle to the anterior wall of a lumbar vertebra, to the posterior wall of the aorta, or to the psoas muscle [18–20], or as the distance between the peritoneum and the lumbar spine [21]. Measurements are always taken in the supine position, with arms at sides. A recent study from our group pointed out that technical issues play an important role in the accuracy and reproducibility of measurements; it is very important to control breathing and fasting state of patients, as well as the pressure of the probe on the skin [14].

3.1.1. Accuracy and reproducibility

The first study aimed to compare CT and ultrasound measurements of adiposity, as performed by Armellini in 1990 [13], resulting in a good correlation between ultrasound thickness measurements and intra-abdominal fat area ($r = 0.669$, $p < 0.001$). Few years later, Tornaghi et al. found that ultrasonographic measurements of the abdominal depth correlated with CT-measured visceral fat area better than others anthropometric indexes ($r = 0.89$-0.91) [22]. Other studies in the subsequent years correlated and validated ultrasound measurements with CT and MRI, confirming a good accuracy [18–23]. However, in the vast majority of studies, linear measurements by ultrasound were correlated with measurements of areas or volumes of fat, detected by CT imaging or MRI. In recent years, some investigators moved to comparative evaluations of linear measurements of CT and ultrasound [9,19,21], finding very good agreement ($r = 0.89$-0.93). Data on reproducibility of IAFT, as for any ultrasound adiposity parameters, are less abundant on scientific literature, and they are expressed and analyzed with different statistical methods. In several studies a coefficient of variation (CV) is reported, ranging generally between 1 and 7% [22]. Stolk et al. [20] found an inter-observer correlation

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Table 1
Definition, accuracy and reliability of ultrasound measurements of adipose tissue.

			Definition	Accuracy and reliability
TISSUE ORGAN LEVEL	VISCERAL FAT THICKNESSES	Intra-abdominal fat tickness	Convex probe (3.5–5 MHz) in the middle line of the abdomen. From the posterior wall of the abdominal muscle to: the anterior wall of the aorta (most authors); the anterior wall of lumbar spine [Leite]; the posterior wall of the aorta [De Lucia Rolfe]; the psoas muscle [Stolk]. One author measured it as the distance between the peritoneum and the lumbar spine [Gradmark].	Good correlation with CT- and MRI- derived areas and volumes. Very good correlation with CT linear measurements. Very good reliability.
		Abdominal Wall Fat Index	Calculated as the ratio between two adiposity thicknesses: maximum pre-peritoneal fat thickness and minimum abdominal subcutaneous fat thickness (see below).	Few, ambiguous data available on accuracy. Good reliability – CV less than 9%.
		Pre-peritoneal Fat Thickness	Linear probe (7.5 MHz) in the upper abdomen, longitudinal scan on the middle line (xiphoumbilical line), just below the xiphoid process, as the major distance between the anterior surface of the peritoneum covering the liver to the posterior surface of linea alba.	Few data on accuracy and reliability.
		Mesenteric Fat Tickness	Convex probe (3.5–5 MHz) on the periumbelical area. When different mesenteric leaves were visualized, the maximum thickness is measured; usually 6–10 measurements are made, and the mean used.	Few and very ambiguous data on accuracy, and reliability.
		Epicardial Fat Tickness	Subjects in left lateral decubitus; ten cycles of two-dimensional parasternal-and short-axis views and 10 cycles of M-mode with optimal cursor beam orientation in each view are required. Epicardial fat thickness appears as an echo-free space on the free wall of the right ventricle from both parasternal long- and short-axis views.	Very good correlations with MRI measurements ($R = 0.905$) and visceral fat area ($R = 0.864$). High intra- and inter- operator reliability with intraclass correlation coefficients ranging between 0.90 and 0.98 and between 0.93 and 0.98, respectively. Concordance of long-axis and short-axis average epicardial fat thickness measurement also excellent with $P = 0.98$ (95% confidence interval, 0.97–0.98) .
		Peri- and para-renal fat tickness	Measured as the distance between the inner side of the abdominal muscle to the surface of the kidney, assessed with a convex probe (3.5–5 MHz), on a longitudinal scan with the surface of the kidney parallel to the skin. Some authors used the value of peri-renal fat alone, assessed with the same method, measuring the thickness between the surface of the kidney and the gerota's fascia [Grima]. One author measured the peri-renal fat distally to the inferior pole of the kidneys [Gong]. Usually the values of both sides are collected and the average value calculated.	Two studies showed a great accuracy with the area of visceral abdominal fat, measured with CT ($P = 0.75$; $p < 0.0001$) [Kavasaki], and with MRI ($P = 0.77$; $p < 0.0001$ [Gong]; this last study also reported an inter- and intra- observer reliability of 0.433 and 0.725 (correlation coefficients). Other studies reported an intraoperator CV ranging from 4.7% and 6.7% and an inter-operator CV of 3.2%.

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Table 1 (*Continued*)

	SUBCUTANEOUS FAT THICKNESSES	Subcutaneous Fat Thickness	SFT is assessed as the distance between the upper border of the dermal/adipose interface and the upper border of the adipose/muscle interface, at the level of measurements; it could be measured at several truncal and appendicular levels; often it is measure at the eight standard ISAK sites. One author measured SAT as the distance from the posterior line of dermis to the outer bowel wall [Gradmark].	Several studies reported a great correlation of SAT-ultrasound measures with: needle puncture measurements; electrical conductivity; MR-derived fat volume of SAT and DXA. Other studies reported a lower correlation with CT-derived fat area. Good reliability: CV between 3.5% and 8.1%, and CC 0.92–0.99.
		Minimum Abdominal Subcutaneous Fat Thickness	Assessed using a linear probe, longitudinal scan on the xiphoumbilical line, in the same anatomic place of maximum preperitoneal fat thickness (just below the xiphoid process in the epigastric region) determined as the distance between the anterior surface of linea alba and the fat-skin barrier.	One study reported a very strong correlation with CT- linear measurements and high reliability [Bazzocchi]. High reliability reported also from another study (intra-observer CV of 4.3% and inter-observer CV of 4.6%) [Hamagawa].
		Maximum Abdominal Subcutaneous Fat Thickness	Measured it as the distance between the linea alba and the fat-skin barrier, with a linear transducer transversely placed perpendicular to the skin in the midline of abdomen, between the xiphoid process and umbilicus [Liu]. Also Kim et al. and Gradmark et al. measured MaxASFT cranial to the umbilicus, 1 cm and 5 cm above, respectively. Bazzocchi et al. instead, measured MaxSFT at two levels: 2 cm above and 2 cm below the umbilicus.	Few studies reported a very good correlation with correlation with CT linear measurements. Coefficient of variation reported to ranging between 3.5% and 8.1%.
INTRACELLULAR FAT CONTENT	Hepatic steatosis		Hepatic steatosis appears on US as a diffuse increase in hepatic echogenicity, usually described as "bright liver. Three diagnostic criteria (all required): - liver echogenicity exceeds that of renal cortex and spleen - loss of definition of the diaphragm - poor delineation of the intrahepatic architecture. Four-point scale for severity: normal (grade 0), mild (grade 1), moderate (grade 2), and severe (grade 3).	In patients without coexisting liver disease, good accuracy for detection of moderate-severe steatosis: (sensitivity 81.8%–100.0% and specificity as high as 98%). Low accuracy in diagnosing hepatic steatosis when all degrees of steatosis were considered (sensitivity 53.3%– 66.6%; specificity 77.0%–93.1%) and when hepatic fibrosis is present. Low intra and inter-observer reliability (between 54.7% and 67.9% and 47.0%–63.7% respectively) using the traditional four-point visual grading system. Higher reliability for computer-assisted quantitative US techniques (computerized hepato-renal index), with a reported sensitivity of 92.7%–100% and a specificity of 91%–92.5%.
	Intramuscular fat		Sarcopenia, the aging-related loss of muscle mass and/or strength, is associated with a qualitative changes in skeletal muscle, included an increase in intramuscular fat and fibrous tissue. Affected muscles appears to have increased ecogenicity (EI) that could be scored visually in a semi-quantitative way or with a computerized quantitative (computer-aided gray-scale analysis).	Few studies on reliability: report of relatively good correlation with electrical impedance myography for the assessment of in Duchenne muscular dystrophy (P = 0.054) [Rutkove], and of a strong correlation with MRI in the assessment of muscular dystrophy. A study found a remarkable difference for inter- and intra- operator reliability between young and old patients (ICCs 57–65% in young; 20–31% in elderly) [Strasser], while another found a very good intra-operator reliability among elderly patients (ICC 0.963 and CV of 4.2%) [Watanabe].

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Table 2
Correlations between ultrasound measurements of adipose tissue and cardio-metabolic risk biomarkers.

Subcutaneous Fat Thicknesses	Association with several clinical and laboratoristic markers of CVD and MS, and significally predicts the presence of MS independent of age, sex, and body mass index. Correlates with total cholesterol and fasting glucose, apolipoprotein B and fasting insulin levels, HDL, cholesterol and tTG levels and IR. Linked with carotid intima–medial thickness (IMT) and ceruloplasmin level and hepatic steatosis. Associated with the presence of metabolic syndrome and hepatic steatosis also in a pediatric population and with the development of gestational diabetes mellitus (GDM) and metabolic syndrome (MS) during pregnancy.
Abdominal wall fat index	Values of abdominal wall fat index > 1 have been found to have elevated TG and total cholesterol levels and decreased flow-mediated vasodilatation. Positively correlates with systolic blood pressure; diastolic blood pressure; TG, LDL cholesterol, total cholesterol levels, and basal insulin levels. Negatively correlates with HDL cholesterol level, insulin sensitivity and leptin level. Absence of correlation was found with total cholesterol level, HDL cholesterol level, insulin sensitivity and carotid IMT, in diabetic patients. Absence of correlation was also found between WFI and coronary artery disease.
Pre-peritoneal fat thickness	Correlates with coronary artery stenosis score, serum total cholesterol, triglyceride, and LDL cholesterol, and negatively correlates with serum HDL cholesterol. Association with increased CVD risk, hypertension, microalbuminuria, retinopathy, IMT and fasting Insulin concentration. Predicts the presence and severity of coronary artery disease and could be associated with arterial stiffness in obese adolescents.
Pre-peritoneal fat thickness	Correlates with coronary artery stenosis score, serum total cholesterol, triglyceride, and LDL, and negatively correlates with serum HDL cholesterol (HDL). Association with increased CVD risk, hypertension, microalbuminuria, retinopathy, IMT and fasting Insulin concentration. Predicts the presence and severity of coronary artery disease and could be associated with arterial stiffness in obese adolescents.
Mesenteric Fat Thickness	Very strong correlation with many clinic and laboratoristic index of metabolic and CV diseases (association with total cholesterol, LDL cholesterol, TG, fasting glucose, glicate hemoglobin levels and systolic blood pressure in men and TG and glicate hemoglobin levels in women). Association with fatty liver, independently of body mass index, age, sex, IR, fasting plasma glucose, lipid and blood pressure. Independently predicts US determined preperitoneal and subcutaneous fat thicknesses as well as of the presence of MS. Linked with MFT and carotid IMT. Associated with an increased risk of OSAS, independent of other abdominal fat thickness, BMI and neck circumference, and with fatty among subjects with Polycystic Ovary Syndrome.
Epicardial Fat Thickness	Associated with HDL and LDL cholesterol levels and inversely associated with insulin sensitivity. Independently associated with blood pressure, LDL cholesterol, fasting glucose, and inflammatory markers. Correlated with the presence of T2DM, with waist circumference, carotid IMT and insulin resistance in adults. Association with left ventricular diastolic function in patients with MS and with carotid IMT, arterial stiffness, and cardiac geometry in children and adolescents. It has been suggest that it could predict coronary plaque composition and the probability of restenosis after coronary stenting.
Peri- and para- renal fat thickness	Associated with chronic kidney disease, increased renal resistance index and hyperuricaemia in type-2 diabetic patients and with early kidney damage in obese patients. Moreover, PeFT and PaFT have been correlated with fat liver infiltration assessed with CT, and with increased ophthalmic artery resistance index and with carotid intima-media thickness in patients with HIV.
Subcutaneous Fat Thicknesses	SFT at thigh level is independently associated with more favorable glucose (in men) and lipid levels (in both sexes). MinASFT has been associated with LDL, HDL and total cholesterol level and with serum leptin level. MinASFT showed no association with coronary artery disease. MaxASFT has been linked with the presence of non alcoolic fatty liver disease (NAFLD).
Hepatic Steatosis	Association with metabolic syndrome, even in non-obese, non-diabetic patients and with abdominal obesity, hypertension, dyslipidaemia (especially high triglyceride and low HDL cholesterol concentrations) and Type 2 diabetes. A strong link has been found between NAFLD and IR, irrespective of obesity. Association with laboratoristic (concentrations of plasma adiponectin, plasma markers of lipid peroxidation, inflammation and endothelial dysfunction) and subclinical markers (carotid artery intima-media thickness, brachial artery endothelial flow-mediated vasodilation, arterial stiffness, intracranial main artery stenosis) of cardio-vascular diseases. Increases incidence of CVD independently of the risk conferred by traditional risk factors and components of MS. Association with CVD and IR found also in children and adolescent populations, in several large epidemiological studies.
Intramuscular fat	Muscle quality assessed with EI using computer-aided gray scale analysis has been found to independently contribute to isometric knee extension strength in middle-aged and elderly women. EI of the thigh muscle reflects muscle strength in elderly men, independently of muscle thickness. On the other hand, muscle echogenicity is not found to be associated with maximum contraction force, a parameter of muscle strength, in elderly men and women.

coefficient of 0.94 ($p < 0.001$), and our research group [9] found an intraclass correlation coefficient (ICC) of 0.96.

3.1.2. Clinical significance

IAFT thickness, collected with ultrasound, was associated with several clinical and laboratoristic markers of CVD and MS, [16,17,24], and this was found as significant predictor of MS, independently of age, sex, and body mass index [24]. A positive correlation with ultrasound-assessed IAFT was found with total cholesterol and fasting glucose [24], apolipoprotein B and fasting insulin levels, high-density lipoprotein (HDL), cholesterol and TG levels [16,24] and IR [16]. IAFT was also linked with two important biomarkers of CVD, the carotid intima–medial thickness (IMT) [16] and ceruloplasmin level, a potent index of coronary artery disease. Another interesting study [15] correlated carotid IMT with the ratio between IAFT and thigh muscle thickness, founding an association, independent of traditional risk factors. A link between IAFT and hepatic steatosis (HS) was also showed [25]. Recent investigations showed a link between metabolic syndrome (MS), HS and ultrasound derived IAFT measures also in pediatric population.

3.2. Abdominal wall fat index

The abdominal wall fat index (WFI), also known as abdominal fat index, is one of the most widely used sonographic indexes for regional adiposity evaluation. This index was proposed by Suzuki

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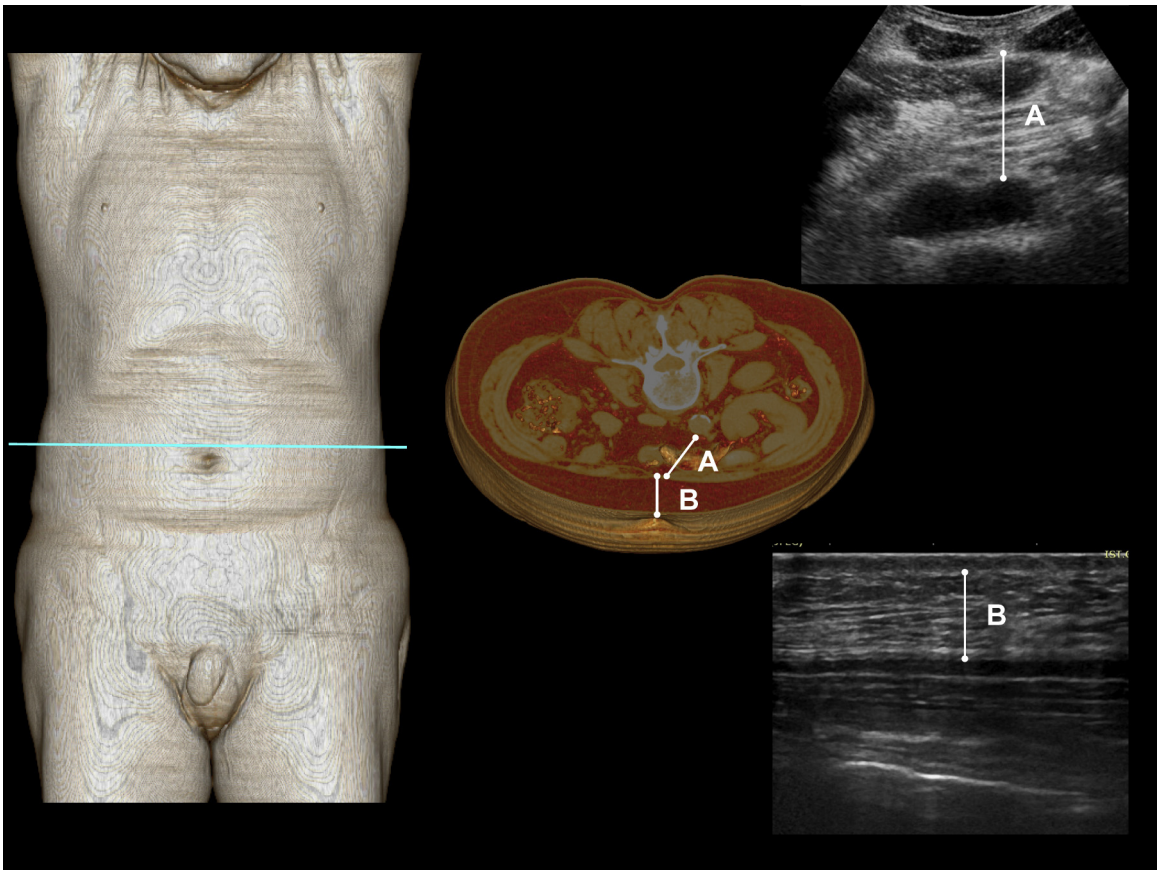

Fig. 1. CT-volume rendering showing the axial level where intra-abdominal fat thickness (A) and maximum subcutaneous fat thickness (B) are studied by ultrasound.

et al. in 1993 [26], calculated as the ratio between two thicknesses: the pre-peritoneal fat thickness (PFT) and the minimum abdominal subcutaneous fat thickness (MinASFT). These two thicknesses are assessed with a linear probe in the upper abdomen, with a longitudinal scan on the middle line (xiphoumbilical line), just below the xiphoid process, as the major distance between the anterior surface of the peritoneum covering the liver to the posterior surface of linea alba (pre-peritoneal fat thickness), and as the distance between the anterior surface of linea alba and the fat-skin barrier (minimum abdominal subcutaneous fat thickness) (Fig. 2).

3.2.1. Accuracy and reproducibility

Few data are available in literature on the accuracy of ultrasound in the evaluation of WFI, with controversial meaning. Suzuki found a strong correlation between WFI and the CT-derived ratio of visceral and subcutaneous fat area ($r = 0.746$; $p < 0.0001$) [26]. Kim et al., on the other hand, found a very weak correlation between a CT-derived measure of visceral area and WFI ($r = 0.101$) [16]. More data are available for reproducibility and repeatability, with more homogeneous results (CV reported to be less than 9%) [16,23,26].

3.2.2. Clinical significance

On the basis of WFI, obesity could be divided in prominently visceral (WFI > 1) or subcutaneous (WFI < 1) type. The former type was found to be associated with elevated TG and total cholesterol levels and decreased flow-mediated vasodilatation, features indicative of elevated cardiovascular risk, despite lower body mass index [23]. Moreover, abdominal WFI was positively correlated with systolic blood pressure, diastolic blood pressure, TG, low density lipoproteins (LDL) cholesterol, total cholesterol levels, and basal insulin levels [23,26,27], and this was negatively correlated with HDL cholesterol level, insulin sensitivity and leptin level [23]. Some studies in female populations found a correlation between WFI and carotid IMT [27], and confirmed the linear correlation with diastolic blood pressure and pulse pressure. On the other hand, in a study by Kim et al. [16], WFI did not show significant correlation with total cholesterol level, HDL cholesterol level, insulin sensitivity and carotid IMT, in diabetic patients. Absence of correlation was also found between WFI and coronary artery disease. The role is therefore controversial.

3.3. Pre-peritoneal fat

Pre-peritoneal fat thickness was introduced by Suzuki et al. in 1995, as part of the WFI [26]. For the assessment of this fat depot, please read above on the WFI section. The classification of pre-peritoneal fat thickness is controversial; many authors consider it as a part of visceral fat depots; however, it extrudes to the systemic blood circulation, rather than to the portal system, thus it is not universally considered a kind of visceral fat [23,28].

3.3.1. Accuracy and reproducibility

Only two studies, to our knowledge, investigated the accuracy of PFT versus the gold standard (CT). The first [16] showed a poor correlation with a CT-derived measure of visceral fat area (Pearson correlation coefficient of 0.328). The second, performed by our group, showed instead a strong correlation between linear measurements of CT and ultrasound (Lin's correlation coefficient of 0.87), with low intra- and inter-observer variability (intraclass correlation coefficients of 0.75–0.90) [9]. The intra-observer coefficient of variation was 4.3% and the inter-observer coefficient of variation was 6.4% in a study by Hamagawa et al. [29].

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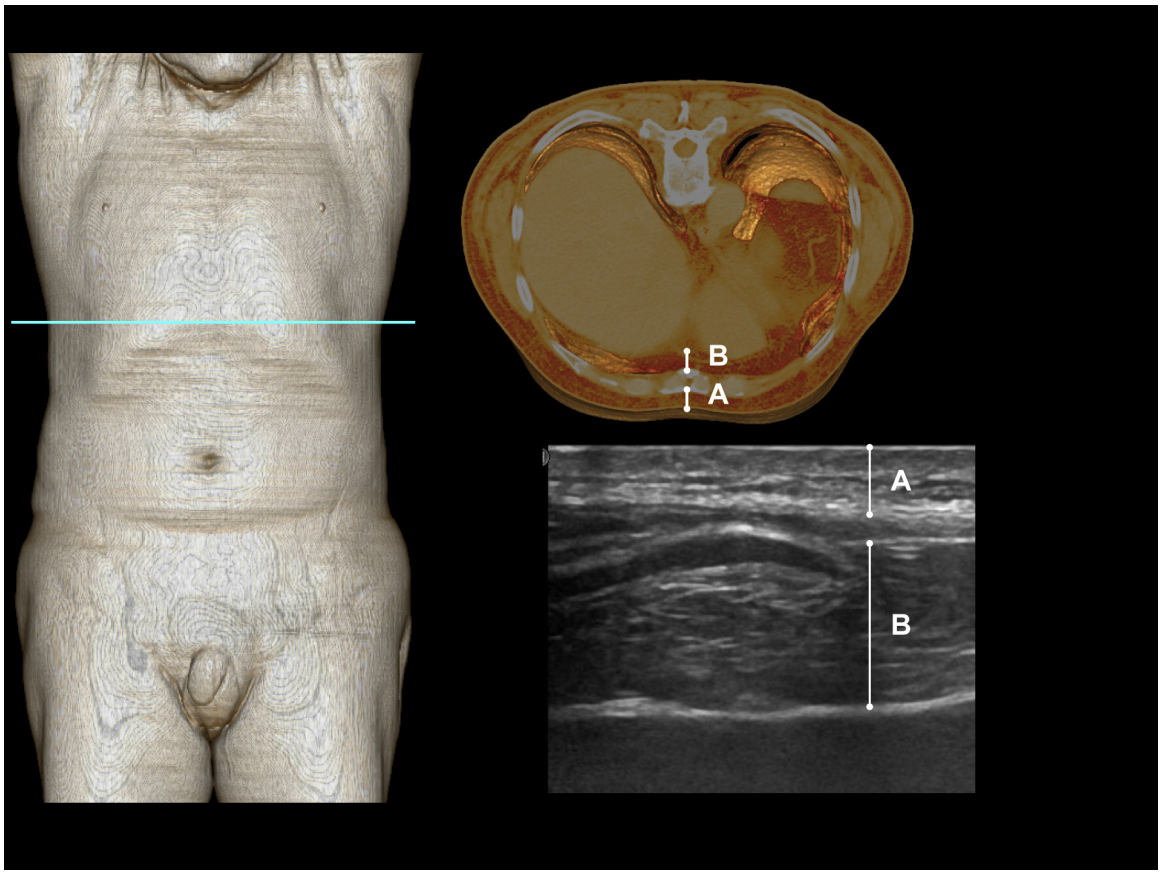

Fig. 2. CT-volume rendering showing the axial level where minimum subcutaneous fat thickness (A) and maximum preperitoneal fat thickness (B) are assessed by ultrasound.

3.3.2. Clinical significance

PFT was found to be positively correlated with coronary artery stenosis score, serum total cholesterol, TG, and LDL, and negatively correlated with serum high HDL cholesterol [30]. Moreover, diabetic patients exhibited a significantly greater deposition of preperitoneal fat than the control subjects [31], and high levels of maximum preperitoneal fat was associated to disease severity, increased CVD risk, and poor prognosis, as shown by the high prevalence of hypertension, microalbuminuria, retinopathy, and elevated levels of hemoglobin [31]. PFT also seems to be correlated with carotid IMT and fasting insulin concentration ($r = 0.37$, $P < 0.005$ and $r = 0.54$, $P < 0.0001$) [32].

Furthermore, recent studies suggested that PFT could predict the presence and severity of coronary artery disease and could be associated with arterial stiffness in obese adolescents [29].

3.4. Mesenteric fat

Mesenteric fat thickness (MFT) is a parameter introduced by Liu et al. in 2003 [28]. MFT is assessed with a convex probe on the periumbelical area, where the mesenteric leaves could be identified as elongated structures with highly reflecting peritoneal surfaces (Fig. 3). When different mesenteric leaves are visualized, the maximum thickness is measured; usually 6–10 measurements are made for each ultrasound examination, and the mean of the three thickest mesenteric leaves is used for the analysis [28]. Mesenteric fat, directly drain to the portal system, leading to increased free fatty acids production because its adipocytes are more sensitive to the lipolytic effects of catecholamines and more resistant to the antilipolytic effects of insulin [28].

3.4.1. Accuracy and reliability

A single study by our group investigated the accuracy of mesenteric fat thickness measurements, using CT as the gold standard, and this found a weak correlation (Lin's correlation coefficient = 0.18) [9], and low intra- and inter-reader agreement values (ICC = 0.17–0.51). A few studies reported stronger reliability, with a work by Liu et al. [28] reporting a very strong ICC coefficient for inter- (0.89) and intra- (0.97) operator agreement. However, these few and variable data question the accuracy and reliability of this parameter.

3.4.2. Clinical significance

Liu et al. proposed several studies showing a very strong correlation between MFT and many clinical and laboratoristic parameters of metabolic and CV diseases. MFT was also positively associated with total cholesterol, LDL cholesterol, TG, fasting glucose, glicate hemoglobin levels and systolic blood pressure in men, and with TG and glicate hemoglobin levels in women [23,28]. In another study of the same research group, MFT was found as a risk factor of fatty liver, independent of body mass index, age, sex, and a promoter of IR, fasting plasma glucose, lipid and blood pressure, with odds ratio of 1.5 for every 1 mm increase in the MFT [33]. MFT was also found to be an independent predictor of ultrasound-measured preperitoneal and subcutaneous fat thicknesses as well as of the presence of MS [34]. Moreover, two studies found a link between MFT and carotid IMT [34]. A recent study stated that MFT is also associated with an increased risk of obstructive sleep apnea syndrome (OSAS) independently of other abdominal fat thicknesses, body mass index and neck circumference [35].

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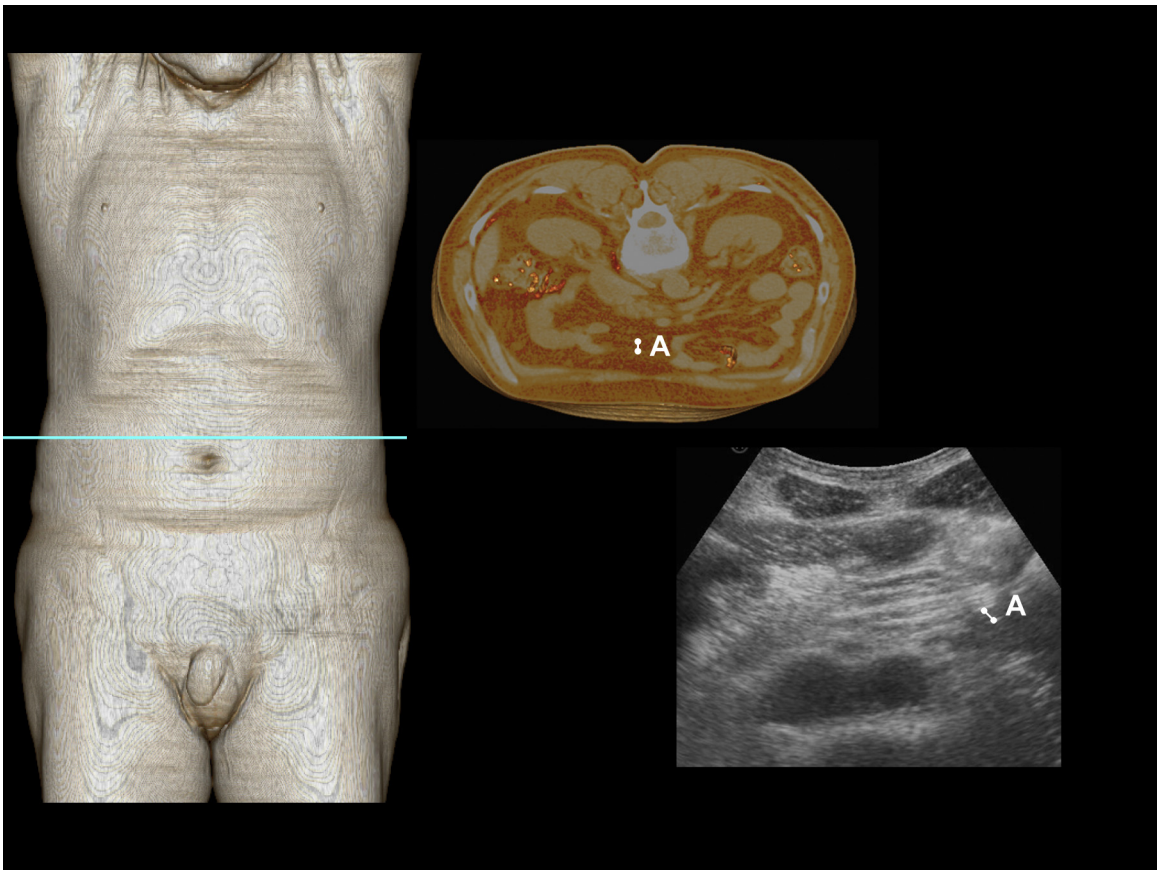

Fig. 3. CT-volume rendering showing the axial level where mesenteric fat thickness (A) is studied by ultrasound.

3.5. Epicardial fat

Epicardial fat is the true visceral fat depot of the heart evolving from brown adipose tissue during embryogenesis [36]. No muscle fascia divides epicardial fat from myocardium, therefore these two tissues share the same microcirculation [36]. Epicardial fat is a source of cytokines with both anti-inflammatory and pro-inflammatory properties, playing a possible role in the adiposity-related inflammation and atherosclerosis. On the other hand, epicardial fat could exert a protective effect through adiponectin and adrenomedullin secretion as response to local or systemic metabolic or protecting against mechanical insults. Epicardial fat thickness is usually assessed with subjects in the left lateral decubitus position; ten cycles of two-dimensional parasternal long-and short-axis views and 10 cycles of M-mode with optimal cursor beam orientation in each view are required. Epicardial fat thickness appears as an echo-free space on the free wall of the right ventricle from both parasternal long- and short-axis views [37]. This parameter is measured on right ventricle because this point is recognized as the highest absolute epicardial fat layer thickness, and because parasternal long- and short-axis views allow the most accurate measurement of epicardial adipose tissue on the right ventricle with optimal cursor beam orientation in each view [37].

3.5.1. Accuracy and reliability

The measurement of epicardial tissue by ultrasound showed a very good correlation with MRI measurements of epicardial fat thickness ($r = 0.905$) and visceral fat area ($r = 0.864$) [37]. Intraclass correlation coefficients ranged 0.90–0.98 and 0.93–0.98, respectively, indicating good reproducibility and reliability. Concordance of long-axis and short-axis average epicardial fat thickness measurement was also excellent (95% confidence interval, 0.97-0.98) [36].

3.5.2. Clinical significance

Epicardial fat thickness in subjects with MS is significantly higher than that observed in subjects without MS [36]. The amount of epicardial adipose tissue is associated with LDL cholesterol levels and inversely associated with insulin sensitivity, as assessed by euglycemic hyperinsulinemic clamp studies in obese subjects [36]. Epicardial fat was also independently associated with blood pressure, fasting glucose, and inflammatory markers [36]. In a recent study, epicardial fat thickness was significantly correlated with the presence of T2DM, waist circumference and carotid IMT, in both sexes, and directly related to surrogate markers of IR as well as fasting insulin and the homeostatic model [38]. Moreover, epicardial fat thickness was correlated with important clinical parameters of cardiac function and CVD risk: it was indeed associated with left ventricular diastolic function in patients with MS, carotid IMT, arterial stiffness, and cardiac geometry in children and adolescents [39].

3.6. Peri- and para- renal fat

Peri-renal fat, also known as perinephric fat, is a kind of adipose tissue that surrounds the kidneys, between the outer surface of the renal parenchyma and the renal (gerota's) fascia; outside the fascia, the kidneys are surrounded by another fat tissue, called para-renal fat, that accumulates mainly posteriorly and postero-laterally to each kidney. Recently, measurements of para- and peri- renal fat thicknesses have been used in a few studies as marker of visceral fat

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accumulation, and correlated to several clinical parameters. They are usually measured as the distance between the inner side of the abdominal muscle to the surface of the kidney (probe 3.5–5 MHz), on a longitudinal scan with the surface of the kidney parallel to the skin [40]. The values of both sides are usually collected and the average value is calculated. Conversely, some studies used the value of peri-renal fat alone, assessed with the same method, measuring the thickness between the surface of the kidney and the gerota's fascia [41]. In a single study the peri-renal fat was measured distally to the inferior pole of the kidneys [42].

3.6.1. Accuracy and reliability

Only two studies correlated ultrasound measures of peri- and para- renal fat with the area of visceral abdominal fat, measured with CT (correlation coefficient of 0.75; $p < 0.0001$) [40], and with MRI (0.77; $p < 0.0001$) [42]; in one of them inter- and intra- observer agreement values of 0.433 and 0.725 (correlation coefficients) were also reported. Other studies reported intra-operator CV ranging 4.7–6.7% and inter-operator CV of 3.2% [40].

3.6.2. Clinical significance

Ultrasound-assessed peri- and para- renal fat were associated with chronic kidney disease, increased renal resistance index and hyperuricaemia in type-2 diabetic patients.

Moreover, peri-renal fat thickness and para-renal fat thickness were correlated with fat liver infiltration assessed with CT ($p < 0.0001$), and two studies in HIV patients correlated peri-renal fat thickness with increased ophthalmic artery resistance index and carotid IMT, markers of CVD risk [41].

3.7. Subcutaneous adipose tissue

The role of subcutaneous fat in the development of obesity-related diseases is controversial. Some studies underlined that subcutaneous fat is much less related with CVD and DM than intra-abdominal fat, and some other hypothesize that subcutaneous fat could be a protective fat depot [7]. On the other hand, few studies found a strong association between subcutaneous abdominal adiposity and IR [8]. From a technical point of view, subcutaneous fat is evaluated with ultrasonography in several anatomic locations, in abdominal and appendicular sites; it has been often measured at the eight standard ISAK sites (International Society for the Advancement of Kinanthrometry). In all these locations, subcutaneous fat is generally measured as the perpendicular distance between the upper border of the dermal/adipose interface and the upper border of the adipose/muscle interface [43]. Only Gradmark et al. measured abdominal SAT as the distance from the posterior line of dermis to the outer bowel wall [21]. In the abdomen, two specific subcutaneous thicknesses are commonly taken into consideration: minimum abdominal subcutaneous fat thickness (MinASFT) and maximum abdominal subcutaneous fat thickness (MaxASFT). MinASFT was first described by Suzuki in 1996, as a part of abdominal wall fat index; MinASFT is defined as the distance between the anterior surface of the linea alba and the fat-skin barrier, in the middle line of the abdomen, just below the xiphoid process (Fig. 2) [26]. MaxASFT was investigated by different authors. Liu et al. measured this as the distance between the linea alba and the fat-skin barrier, with a linear transducer transversely placed perpendicular to the skin in the midline of abdomen, between the xiphoid process and umbilicus (Fig. 1) [28]; Kim et al. and Gradmark et al. measured MaxASFT cranial to the umbilicus, 1 cm and 5 cm above, respectively [16,21]; our group provided MaxASFT at two levels: 2 cm above and 2 cm below the umbilicus [9].

3.7.1. Accuracy and reliability

About 50 years ago, researchers reported very strong correlations between SFT ultrasound measurements and needle puncture measurements ($r = 0.98$), and electrical conductivity ($r = 0.98$). Between the 60′s and the 80′s several studies tested ultrasound versus skinfolds calipers to verify which method had higher accuracy in the measurement of subcutaneous fat, finding uncertain results.

In a 2007 study by Koda et al. ultrasound measurements of SFT were closely correlated to subcutaneous fat volume by serial-slice MR imaging ($r = 0.816$, $p < 0.0001$) [44]. In 2012, Leahy et al. found that a single ultrasound measure of subcutaneous adipose tissue at the abdomen in 83 men and 52 women was highly correlated to body fat percentage assessed with DXA in both men ($r = 0.907$) and women ($r = 0.905$) [45].

Abe et al. correlated total and segmental subcutaneous adipose tissue volumes derived from ultrasound and MRI measurements, finding strong correlations (0.75–0.95) [46].

On the other hand, two studies showed poor correlation between ultrasound and CT measurements for SFT. For Gradmark et al. [21], the ultrasound measures of subcutaneous fat were less correlated to the total subcutaneous area assessed by CT, than waist/height ratio and DXA and body mass index, but measurements of SAT with ultrasound were very closely associated with CT linear measurements (Lin 0.90); a study of our group came to similar results, finding very high correlation between CT-linear measurements and ultrasound measures of MinASFT and MaxASFT (Lin 0.95–0.98) [9]. There are few data on reproducibility of subcutaneous thickness measurements with ultrasound. A study of our group found very strong inter- and intra-operator agreements for 3 different subcutaneous fat levels in the abdomen [9]. Muller et al. investigated the reliability of SFT measurements at eight ISAK sites, with inter-observer coefficients ranging from 0.92 to 0.99 [47], while Kim et al. found a coefficient of variation for MaxASFT and MinASFT between 3.5% and 8.1% [16].

Hamagawa et al. found an intra-observer CV for MinASFT of 4.3% and an inter-observer CV of 4.6% [29].

3.7.2. Clinical significance

Sonographic indexes of subcutaneous fat thickness were rarely correlated to clinical and laboratoristic parameters of metabolic disorders and CVD. Some studies took in consideration MinASFT, finding an association with LDL, HDL and total cholesterol level and with serum leptin level [23].

On the other hand, studies showed that MinASFT is not associated with coronary artery disease [29].

One interesting article showed a link between subcutaneous abdominal thickness and the presence of non alcoolic fatty liver disease (NAFLD) [48], while another research showed that a larger subcutaneous fat depot at thigh level is independently associated with more favorable glucose (in men) and lipid levels (in both sexes) [49].

4. Organ-specific evaluation of intracellular fat content

All organs are involved in the management and modulation of human metabolism, however some act as primary player, other are secondary being less influential in direct regulation of metabolism while submitted to its changes and its potential defects, or diseases. Organs play roles from intake, to storing, burning, and expending of energy and these roles are still not completely understood. Metabolic diseases may alter the function of an organ, as well as an independent organ disorder may alter and affect metabolic processes. Apart from adipose tissues, the liver is certainly one of the leader in the management of human metabolism as well as the

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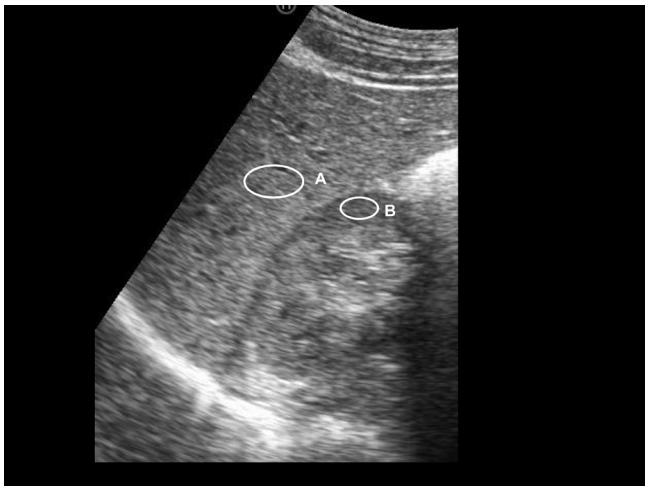

Fig. 4. Liver echogenicity (A) compared to renal cortex (B).

skeletal muscle is a depot of lipid accumulation and clearly one of the most demanding users and consumers of energy in the body. Thus, in the context of this paper a rapid overview of potentials of ultrasound in the body composition analysis of the liver and the skeletal muscle is be presented.

4.1. Liver and fatty liver diseases

Hepatic steatosis (HS), or fatty liver, is the term used to describe a spectrum of conditions in which TG accumulates within hepatocytes [50]. Alcohol is a well-known cause of fatty liver disease in adults, and can manifest histologically as steatosis, steatohepatitis, and cirrhosis. In more recent years, another entity, non-alcoholic fatty liver disease (NAFLD), was delineated and defined, mimickingthe entire spectrum of hepatic changes typically associated with alcohol abuse. NAFLD is associated with MS, obesity, IR and hypertension and is one of the most common causes of chronic liver diseases in Western countries, occurring in approximately 30% of the general population. The progression from NAFLD to cirrhosis through the development of non-alcoholic steatohepatitis (NASH) and fibrosis has been established, even if exact risk of this progression has still to be determined, being estimated in about 10–25% of patients [51].

To determine increased liver intracellular fat content, liver biopsy is currently considered the gold standard, but it suffers from several limitations, first of all its invasivity, and second the small and partial sampling of the tissue.

Various imaging techniques have been developed for this aim, such as ultrasonography, CT, MRI and magnetic resonance spectroscopy (MRS).

4.1.1. Accuracy and reliability

Hepatic steatosis appears on ultrasound as a diffuse increase in hepatic echogenicity, usually described as “bright liver” [51]. Fatty liver may be diagnosed if all these three conditions are fulfilled: liver echogenicity that exceeds that of renal cortex and spleen with attenuation of the ultrasound wave, loss of definition of the diaphragm, and poor delineation of the intra-hepatic architecture (Fig. 4) [50]. Severity is usually graded using a four-point scale, as follows: normal (grade 0), mild (grade 1), moderate (grade 2), and severe (grade 3) [51]. The accuracy of ultrasound in the detection of fatty liver was reported to vary depending on the severity of HS and the presence of other coexisting chronic liver diseases. In patients without coexisting liver diseases, ultrasound offers a fairly accurate diagnosis of moderate-to-severe HS, with sensitivity ranging between 81.8% and 100.0% and specificity as high as 98% [51]. On the other hand, ultrasound showed low accuracy in diagnosing HS when all degrees of steatosis were considered (sensitivity 53.3% –66.6%; specificity 77.0%-93.1%) [51]. Indeed, the sensitivity for detecting mild degrees of steatosis is low, ranging from 55% to 90%. As fibrosis usually increase hepatic echogenicity the presence of underlying chronic liver disease may reduce the accuracy of ultrasound in the diagnosis of HS [51]. Some studies also found a low sensitivity of ultrasound in the detection of HS in obese patients. A major limitation of ultrasound is the low intra- and inter-observer agreements, which are reported to vary between 54.7% and 67.9% and 47.0%–63.7%, respectively, when assessing the severity of HS using the traditional four-point visual grading system [51]; inter-operator reproducibility for the assessment of the presence/absence of steatosis is of course higher, reported to be respectively 70–73% [52]. Another limitation of ultrasound is the qualitative nature of the current four-point grading system, too subjective to account for small alterations in steatosis severity, or during a follow-up. To overcome these limitations, some computer-assisted quantitative ultrasound techniques were developed for the assessment of HS [51]; among them, the computerized hepato-renal index is the most used. It consists in a computerized correlation of liver ecogenicity with that of the right kidney cortex. The results of two related studies were very promising, with a reported sensitivity of 92.7% and 100% and specificity of 91% and 92.5% in diagnosing HS $\geq$ 5% [53].

4.1.2. Clinical significance

Although accuracy of ultrasound in the detection of mild steatosis is not good as desirable, and although the agreement with histopathology is not excellent, ultrasound do have many and robust advantages compared to other methods in the assessment of HS: it is fast, available, cheap, totally non-invasive and well-tolerated by patients, therefore it is particularly useful in large epidemiological studies. Many of these large studies showed a strong correlation between hepatic steatosis detected with ultrasound and MS, even in non-obese, non-diabetic patients [54]. Abdominal obesity, hypertension, dyslipidaemia (especially high TG and low HDL cholesterol concentrations) and Type 2 diabetes are pathological conditions frequently associated with NAFLD, and their coexistence within the same individual increases the likelihood of having more advanced forms of liver disease [55]. Additionally, a strong association was found between NAFLD and IR, irrespective of obesity [55].

HS has been associated also with laboratoristic (concentrations of plasma adiponectin, plasma markers of lipid peroxidation, inflammation and endothelial dysfunction) and subclinical markers (carotid artery intima-media thickness, brachial artery endothelial flow-mediated vasodilation, arterial stiffness, intracranial main artery stenosis) of CVD [54,55].

Unsurprisingly, given these associations with markers of CVD, HS was also associated with an increased incidence of CVD [54,55], and recent epidemiological studies in adult subjects also demonstrated that NAFLD is associated with an increased risk of incident CVD that is independent of the risk conferred by traditional risk factors and components of MS [51].

Moreover, CVD and IR were also associated with ultrasound-detected HS in children and adolescent populations, in several large epidemiological studies [51,56].

4.2. Muscle and “fatty muscle disease”

It is well known that muscles affected by a neuromuscular disease have a distinctive appearance at ultrasonography. As well, non-used muscle after trauma or in other condition of sarcopenia have such appearance. Besides a diminished muscle thickness,

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affected muscles also appear to have increased echo intensity (EI), due to an excessive intramuscular fat, intramyocellular TG levels, and non-contractile infiltrates.

These muscle alterations, detected by ultrasonography, have been described in a variety of neuromuscular disorders, such as myositis, motor-neuron disease, muscular dystrophy, congenital myopathy, polyneuropathy and sarcopenia.

The latter, sarcopenia, defined as the aging-related loss of muscle mass and/or strength, is indeed associated with a qualitative changes in skeletal muscle, including an increase in intramuscular fat and fibrous tissue; it is an important condition, and a primary factor in the development of frailty, accounting for falls and loss of independence; it was also associated with lifestyle-related diseases, osteopenia, and mortality risk [57].

Muscle EI could be scored visually in a semi-quantitative way; however recently tools for computerized quantitative analyses have been developed and are evolving as the current standard. Quantitative analysis of EI can be achieved by computer-aided gray-scale analysis or using grayscale histogram [57].

4.2.1. Accuracy and reliability

Accuracy of ultrasound in the assessment of muscular EI have been rarely compared with other techniques in literature. A recent study correlated ultrasound-assessed muscle EI with electrical impedance myography for the assessment of Duchenne muscular dystrophy, finding relatively good correlation (P = 0.054) [58]. Focusing on reproducibility, a study found a remarkable difference for inter- and intra- operator variability between young and old patients (ICCs 57–65% in young; 20–31% in elderly) [59], while another study found a very good intra-operator agreement for elderly patients (ICC 0.963 and CV 0f 4.2%) [57].

4.2.2. Clinical significance

Several articles reported a strong association between ultrasound muscle EI and the presence of muscular dystrophy, in particular Duchenne muscular dystrophy.

More recently some studies also investigated the relation between muscle EI and muscle strength, especially in elderly population, to study sarcopenia. Fukumoto et al. [60] reported that muscle thickness of the knee extensor and muscle quality assessed with EI measured using computer-aided gray scale analysis independently contribute to isometric knee extension strength in middle-aged and elderly women. Watanabe et al. showed that muscle EI of the thigh reflects muscle strength in elderly men ($r = -0.333$, $P = 0.001$), independently of muscle thickness [57]. However, a very interesting study by Strasser et al. [59] found opposite results; compared muscle thickness, pennation angle, echogenicity and skeletal muscle strength of the quadriceps muscle in the elderly and found that muscle EI was not associated with maximum contraction force, a parameter of muscle strength. More studies are needed to investigate the role of muscle EI in the evaluation of muscle strength and sarcopenia.

5. Conclusion

Ultrasound is a non-invasive, fast, relatively inexpensive and available tool for estimating adiposity in clinical practice, and in several research settings. It does not expose patients to ionizing radiation risks, making the method ideal for the evaluation in young patients, and for follow-up studies. Several parameters and indexes of adipose tissue thicknesses have been introduced and tested, and correlated with clinical and laboratoristic parameters. Intracellular fat depots can also be assessed in other organs (e.g. liver, muscle). However, standardized procedure and parameters are needing to improve accuracy, reproducibility and to support studies. More homogenous data and robust research projects should be provided about the association of ultrasound parameters with patient function and prognosis.

Conflict of interest

None.

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