Review

Adipose Tissue Radiodensity in Chronic Diseases: A Literature Review of the Applied Methodologies

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ABSTRACT

Background: The concept of adipose tissue radiodensity is emerging and its relationship to disease prognosis has been infrequently explored. The aims of the present study were to evaluate published literature that explored adipose tissue radiodensity in relation to outcomes in health and disease and to summarize methodologies used to evaluate adipose tissue radiodensity by computed tomography (CT).

Methods: A comprehensive literature review included all published studies that applied CT imaging of the abdominal region to define adipose tissue radiodensity. The review was performed without regard for study design or quality.

Results: We identified 22 studies that evaluated the relationship between adipose tissue radiodensity and outcomes. The literature reviewed highlights significant methodological variation in terms of abdominal region selected, slice thickness, contrast media, dose, software, and radiodensity ranges used to define adipose tissues. This is primarily due to a lack of consensus about the effect such methodological variables have on body composition parameters.

Conclusions: Authors should carefully report adipose tissue radiodensity, especially when it comes to prognosis inference. Consensus on methodology will enable meaningful advancement in understanding the importance of adipose tissue radiodensity in different disease conditions.

KEYWORDS: adipose tissue; computed tomography; VAT; SAT; radiodensity

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INTRODUCTION

Computed tomography (CT) based image analysis enables the precise quantification of body composition and different body compartments, particularly adipose tissue, and skeletal muscle (SM). CT is opportunistically applied in the patient populations that require CT

imaging as part of standard assessment for diagnosis or treatment and is considered the gold standard for body composition assessment in clinical research [1,2]. CT imaging uses Hounsfield units (HU), a radiological unit of measure, to differentiate tissues. To date, CT imaging has revealed that SM loss (atrophy) and muscle with low radiodensity (an indicator of fatty infiltration of muscle known as myosteatosis) are prevalent in people with different chronic diseases [3], and each of these features have been independently associated with reduced overall survival (OS) in cancer patients [4]. Several studies have reported associations between low muscle radiodensity, all-cause mortality, and systemic inflammation in cancer patients [4–12], as well as in other chronic diseases [3]. However, little is known about adipose tissue radiodensity, also defined as adipose tissue attenuation or fat attenuation. In experimental models, lower adipose tissue radiodensity (HU) is associated with higher adipose tissue lipid content [13], this is also supported by a radiologic finding from a small pediatric population [14]. In contrast, adipose tissue with higher radiodensity is indicative of relatively lower lipid content and higher vascularity [13,15], and possible deposition of extracellular matrix [16]. Therefore, adipose tissue radiodensity may provide an indirect measure of tissue lipid depletion and composition since adipose tissue is composed of adipocytes whose main function is to store energy in the form of triglyceride (TG).

Adipose tissue is a metabolically dynamic organ that synthesizes biologically active compounds and regulates metabolic homeostasis [17]. Fat loss is associated with poor prognosis in patients with advanced cancer, independent of body weight [18]. Two major depots of adipose tissue, visceral (VAT) and subcutaneous (SAT) adipose tissue, differ by location as well as metabolic functions [19]. VAT and SAT behave differently in the last year of life in cancer patients [20]. Higher subcutaneous adiposity, measured by CT, was associated with lower mortality risk in cancer patients [20,21]; likewise, in cirrhosis, lower adiposity in the subcutaneous region was associated with higher mortality in female patients but not in male patients, suggesting possible sexual dimorphism associated with CT-based fat measures [22]. On the other hand, inconsistent associations between visceral adiposity and cancer survival have been reported [6,23,24]. The measure of adipose tissue radiodensity, revealed by CT imaging, adds a new level of complexity to understanding the importance of fat depots in relation to survival.

Limited studies exist to associate CT-derived adipose tissue radiodensity with distinct health outcomes in different disease conditions, including cancers [25–33], metabolic complications [34–44], as well as other health conditions [45,46]. When applied to evaluation of muscle radiodensity, CT-derived studies show variable approaches regarding the evaluation of different body regions, muscle groups, different radiodensity boundaries and in use of contrast agents [47,48]. Whether similar variability is prevalent for measures of adipose tissue radiodensity

in the literature is not known. The objectives of this review are to summarize the CT-based approaches performed in different health conditions to evaluate adipose tissue radiodensity (VAT and SAT) in humans and evaluate variability in methodologies to bring consensus to evaluation of adipose tissue radiodensity as an emerging prognostic factor.

METHODS

Search Strategies

Guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [49,50] were used to conduct the literature search. PRISMA search strategies are shown in Figure 1. An electronic literature search of peer-reviewed journal articles was conducted using Scopus and U.S. National Library of Medicine (PubMed). Manuscripts indexed from January 1, 1990 to March 31, 2021 were queried. Databases were searched using following terms (VAT Radiodensity) OR (SAT Radiodensity) OR (fat radiodensity) OR (adipose tissue radiodensity) OR (lipid radiodensity) OR (VAT Hounsfield unit) OR (SAT Hounsfield unit) OR (fat Hounsfield unit) OR (adipose tissue Hounsfield unit) OR (lipid Hounsfield unit).

Eligibility Criteria

Review articles, studies on experimental models, articles published in a language other than English, articles not available as full text, studies which did not use CT, and studies which used CT and measured abdominal fat but did not report radiodensity measures were removed from further consideration. Peer-reviewed original research articles were included regardless of study type (i.e., retrospective, prospective, or cross sectional) and there were no exclusion criteria regarding number of patients nor study quality. For the selection process (Figure 1), the first researcher systematically assessed the eligibility of each study resulting from database searches based on title and abstract reading. The complete selected articles were carefully reviewed by reading full text. Articles were discussed with the study team and eligibility was determined by consensus, if needed. A hand search of the reference lists from identified articles was carried out to find additional relevant publications. Data were extracted from the result sections, tables, and figures of each article. Full texts of eligible studies were reviewed by the investigators against the inclusion and exclusion criteria and any disagreements were resolved by consensus among authors.

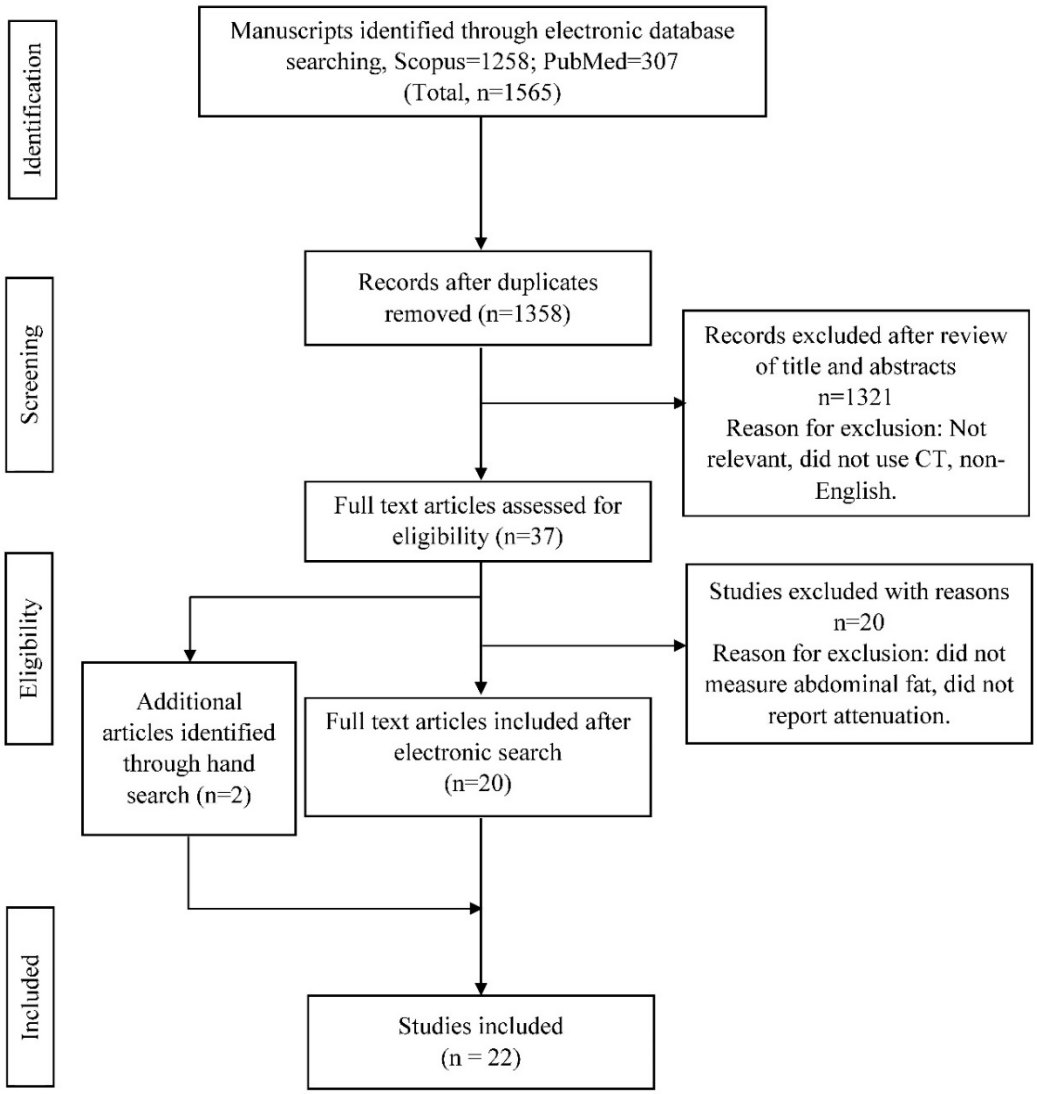

Figure 1. PRISMA flow chart for the identification, screening, eligibility and inclusion of manuscripts.

RESULTS

A comprehensive literature review was conducted to firstly understand what is known about fat attenuation in the published literature. Twenty-two studies met inclusion criteria (Table 1). All studies measured VAT and SAT radiodensity except for two studies those only reported SAT radiodensity [29,46]. Nine studies evaluated VAT and/or SAT radiodensity in oncology patients [25–33]. Other studies assessed CVD risk factors and/or CVD associated mortality (8 studies) [34,36,37,40,42,44,45]; weight change (2 studies) [38,39]; mortality risks in older adults (1 study) [35], risk of type II diabetes (1 study) [43], and risk of hypertriglyceridemia-induced pancreatitis severity (1 study) [46] (Table 1).

Table 1. Published studies reporting adipose tissue radiodensity.

Ref	Participant	Age and Sex Distribution	Instrument Used	Region Used	Thickness of Slice	Contrast Used	Dose (voltage/ current)	Software Used	Study Outcome
[25]	Extremity sarcoma	Male, *n* = 86, age = 50.7 ± 17.0 years Female, *n* = 49, age = 50.8 ± 17.8 years	Siemens Biograph 16 or 64, (Siemens, Erlangen, Germany or GE Healthcare discovery, Milwaukee, Wisconsin, USA)	Remote from the site of sarcoma	5 mm	non-contrast	120 kVp/11 mA	Osirix version 3.2.1(Pixmeo, Geneva, Switzerland)	↑ mortality in ♀♂ associated with ↑ SAT radiodensity but not with VAT
[26]	Extremity soft tissue sarcoma	*n* = 60, male, *n* = 32, female, *n* = 28, age = 50 ± 18 years	Whole-body 18-F-FDG-PET/CT (Siemens Biograph 16 or 64, Siemens, Erlangen, Germany or GE Discovery, GE Healthcare, Milwaukee, WI, USA)	L4	5 mm	non-contrast	120 kVp/11 mA	Osirix version 3.2.1(Pixmeo, Geneva, Switzerland)	↑ post-surgical wound infections in ♀♂ associated with ↑ SAT and VAT radiodensity, however, VAT radiodensity lost significance after adjustment for covariates ↑ tumor recurrence in male and female associated with ↑ SAT radiodensity only

Table 1. *Cont.*

Ref	Participant	Age and Sex Distribution	Instrument Used	Region Used	Thickness of Slice	Contrast Used	Dose (voltage/ current)	Software Used	Study Outcome
[27]	Soft tissue sarcoma	*n* = 137, mean age = 53 ± 17.7 years; male, *n* = 75, female, *n* = 62	N/R	L4	N/R	N/R	N/R	ImageJ (v1.42q, NIH, USA)	Both VAT and SAT radiodensity had no association with OS
[28]	Pancreatic adenocarcinoma	*n* = 66, male 36, female 30, mean age = 66 years	Biograph mCT 128 scanner (Siemens Healthcare, Knoxville, TN, USA)	L4	N/R	non-contrast	120 kVp/100 mA	Osirix MD 9.0 (Pixmeo; Geneva, Switzerland)	↓ OS in ♀♂ associated with ↑ SAT and VAT radiodensity
[29]	Prostate Cancer	Male, *n* = 171, age = 66.0 ± 8.1 years	Varian Eclipse (Varian Medical Systems, Palo Alto, CA)	L4-L5 vertebral interface	N/R	N/R	N/R	Eclipse CT ranger tool	↓ SAT radiodensity was associated with a ↓ rate of biochemical failure following radiotherapy
[30]	Head and neck cancer	*n* = 152, male 128, female 24, mean age = 62 years	Biograph mCT 128 scanner (Siemens Healthcare, Knoxville, TN, USA)	L4	N/R	non-contrast	120 kVp/100 mA	OsiriX MD 9.0 (Pixmeo, Geneva, Switzerland)	↓ progression-free survival and distant failure-free survival in ♀♂ associated with ↑ VAT radiodensity but not with SAT

Table 1. *Cont.*

Ref	Participant	Age and Sex Distribution	Instrument Used	Region Used	Thickness of Slice	Contrast Used	Dose (voltage/ current)	Software Used	Study Outcome
[31]	Esophageal cancer	*n* = 145, male 109, female 36, median age = 60.3 years	N/R	L3	N/R	non-contrast	N/R	PLANET Onco software (DOSIsoft, Cachan, France)	↓ VAT and SAT radiodensity associated with better OS
[32]	Hepatocellular carcinoma	*n* = 101, male 89, female 12, mean age = 62.0 ± 12 years	N/R	L3	N/R	non-contrast	N/R	SliceOmatic (V4.2; Tomovision, Montreal, QC, Canada)	↑ VAT radiodensity associated with ↑ mortality and severe adverse events
[33]	Multiple myeloma	*n* = 91, male 52, female 39, mean age = 64.0 ± 11 years	Siemens Biograph TruePoint mCT 40 (Siemens Healthcare, USA)	L3	2.1 mm	non-contrast	120–140 kVp/120 mA	SliceOmatic (V5.0; Tomovision, Montreal, QC, Canada)	↑ SAT radiodensity associated with ↓ OS and event-free survival
[34]	Apparently healthy	Male, *n* = 1680, age 49.6 ± 10.6 years Female, *n* = 1518, age = 51.9 ± 9.8 years	N/R	N/R	5 mm	N/R	N/R	N/R	↑ adverse cardiometabolic risk in ♀♂ associated with ↓ VAT and SAT radiodensity

Table 1. *Cont.*

Ref	Participant	Age and Sex Distribution	Instrument Used	Region Used	Thickness of Slice	Contrast Used	Dose (voltage/ current)	Software Used	Study Outcome
[35]	Apparently healthy elder	Study 1: Male, *n* = 1345, age 73.5 ± 2.9 years Female, *n* = 1390, age 73.5 ± 2.9 years Study 2: male, *n* = 2207, age = 76.6 ± 5.3 years female, *n* = 2924, age = 76.4 ± 5.5 years	Study 1: Somatom Plus 4 scanners (Siemens, Erlangen, Germany); PQ 200S (Marconi Medical Systems, Cleveland, OH); 9800 Advantage (General Electric, Milwaukee, WI) Study 2: Sensation; Siemens Medical Systems)	L4/L5 vertebrae interface	10 mm	N/R	N/R	Interactive Data Language software (ITT Visualization Solutions, Boulder, CO, USA)	↑ death risk in ♀♂ associated with ↑ VAT and SAT radiodensity
[36]	Apparently healthy	*n* = 3079, male, *n* = 1516, age = 51.6 ± 9.5 years; female, *n* = 1563, age = 48.7 ± 10.1 years	LightSpeed Ultra; General Electric, Milwaukee, WI	N/R	5 mm	N/R	N/R	Aquarius 3D Workstation (TeraRecon Inc., San Mateo, CA)	↓ risk of subclinical atherosclerosis in ♀♂ associated with ↓ SAT and VAT radiodensity
[37]	Apparently healthy	*n* = 1730; male, *n* = 958, age = 44.1 ± 6.3 years female, *n* = 772, age = 46.0 ± 5.7 years	Discovery VCT 64-slice PET/CT scanner (GE Healthcare)	2 cm above the S1 vertebra	5 mm	N/R	120 kVp/100–300 mA	Aquarius 3D Workstation (TeraRecon Inc., San Mateo, CA)	↑ adverse metabolic profiles at follow-up in ♀♂ associated with ↓ VAT and SAT radiodensity

Table 1. *Cont.*

Ref	Participant	Age and Sex Distribution	Instrument Used	Region Used	Thickness of Slice	Contrast Used	Dose (voltage/ current)	Software Used	Study Outcome
[38]	Apparently healthy	Male, *n* = 500, age = 44.3 ± 5.9 years; female, *n* = 366, age = 47.7 ± 5.8 years	Aquarius 3D Workstation software (TeraRecon Inc., San Mateo, CA, USA)	12.5 cm above the S1 vertebra	5 mm	N/R	N/R	N/R	↑ weight gain in ♀♂ associated with ↓ VAT and SAT radiodensity
[39]	Obese	Female, *n* = 38; obese, *n* = 23, age = 42.8 ± 9.6; non-obese, *n* = 15, age = 44.8 ± 12.4 years	Discovery VCT (VCT) PET/CT system (General Electric Medical Systems, Milwaukee, WI, US	T12-S1 vertebra	0.625 mm	N/R	120 kVp/50 mA	Carimas (version 2.9, Turku PET Centre)	↑ VAT and SAT radiodensity correlated negatively with the decreased levels of ApoB/ApoA-I ratio, leucine and GlycA
[40]	Apparently healthy	*n* = 1106, baseline age = 45.1 ± 6.2 years; male, *n* = 618; female, *n* = 488	LightSpeed Ultra (General Electric, Milwaukee, Wisconsin)	N/R	5 mm	N/R	N/R	Aquarius 3D Workstation (TeraRecon Inc., San Mateo, CA)	↑ CVD risk factors in ♀♂ associated with ↓ VAT and SAT radiodensity

Table 1. *Cont*.

Ref	Participant	Age and Sex Distribution	Instrument Used	Region Used	Thickness of Slice	Contrast Used	Dose (voltage/ current)	Software Used	Study Outcome
[41]	Apparently healthy	Male, *n* = 1008, age 44.1 ± 6.3; female, *n* = 821, age = 46.1 ± 5.7 years	LightSpeed Ultra (General Electric, Milwaukee, WI)	N/R	5 mm	N/R	120 kVp/N/R	Aquarius 3D Workstation (TeraRecon Inc, San Mateo, CA, USA)	↑ cardiometabolic risk biomarkers in ♀♂ associated with ↓ VAT and SAT radiodensity
[42]	Apparently healthy	*n* = 1511, Male and female specific age not defined	Electron-beam CT (Imatron C-150), Multi-detector CT scanners (Sensation 64, GE Lightspeed; Siemens S4 Volume Zoom; and Siemens Sensation 16)	N/R	6 mm	N/R	N/R	MIPAV 4.1.2 software (NIH, USA)	↓ incident metabolic syndrome, circulating inflammatory biomarkers and insulin resistance in ♀♂ associated with ↑ VAT radiodensity
[43]	Apparently healthy	Male, *n* = 505, median age = 61 years	NX/I CT scanner (GE Medical Systems, Waukesha, Wisconsin)	L4-L5 vertebral interface	3 mm	non-contrast	120 kVp/250–300 mA	OsiriX (Pixmeo, Geneva, Switzerland)	↑ insulin and insulin resistance associated with ↓ VAT and SAT radiodensity

Table 1. *Cont.*

Ref	Participant	Age and Sex Distribution	Instrument Used	Region Used	Thickness of Slice	Contrast Used	Dose (voltage/ current)	Software Used	Study Outcome
[44]	Undergoes abdominal hysterectomies or myomectomy	Female, *n* = 241, age 47 ± 5.2 years	GE Light Speed 1.1 CT scanner or the Brightspeed CT scan (General Electric Medical Systems, Milwaukee, WI)	L4-L5 vertebrae interface	5 mm	N/R	N/R	Image J 1.33u (NIH, USA)	↑ fat cell weight and cardiometabolic risk profile associated with ↓ VAT and SAT radiodensity
[45]	Apparently healthy	Male, *n* = 1721, age 49.7 ± 10.7 years Female, *n* = 1603, age = 52.2 ± 9.9 years	N/R	N/R	5 mm	N/R	N/R	N/R	↑ All cause mortality, cancer mortality in ♀♂ associated with ↓ VAT and SAT radiodensity
[46]	Acute pancreatitis	*n* = 242, mean age = 40 years; male, *n* = 193; female, *n* = 49	64-slice spiral CT scanner (Lightspeed VCT, GE healthcare, USA) or Aquilion ONE 320 Slice CT scanner (Toshiba, Japan)	L3	0.625 mm and 0.5 mm	contrast-enhanced	120 kVp/300–500 mA	Image J (NIH, USA)	SAT radiodensity was not associated with hypertriglyceridemia -induced pancreatitis severity

Abbreviations: N/R, not reported; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; OS overall survival; ♀, female; ♂, male; ↑, significant increase; ↓, significant decrease; GlycA, glycine and glycoprotein acetyls; kVp, kilovoltage peak; mA, milliampere; T12, 12th thoracic vertebrae; S1, 1st sacral vertebrae.

Use of Abdominal Region for CT Analysis

Different abdominal regions were used to determine adipose tissue radiodensity. Four studies (18.2%) measured radiodensity from L3 [31–33,46]; four studies from L4 [26–28,30]; and four studies from L4/L5 region [29,35,43,44], respectively. One study measured from 2 cm above the S1 vertebra [37]; one 12.5 cm above the S1 vertebra region [38]; one T12-S1 vertebra region [39]; and one study did not specify area but mentioned remote area from the site of sarcoma [25]. In contrast, six (27.3%) studies did not report the region used for CT measurement (Table 1). The rationale for using one region over another was not provided in any of the studies.

Use of Slice Thickness for CT Analysis

Studies have applied different slice thickness to their analysis. Ten studies (45.5%) used 5mm slice thickness [25,26,34,36–38,40,41,44,45]; one study (4.5%) used 10 mm [35], one study 0.625 mm [39]; one study used 6 mm [42]; one study 3 mm [43]; one study both 0.625 and 0.5 mm [46]; and another study used 2.1 mm slice thickness [33]. Six studies (27.3%) did not report slice thickness [27–32] (Table 1).

Use of Contrast Agents for CT Analysis

Most studies (13 out of 22; 59.1%) did not report whether they used contrast or non-contrast CT images [27,29,34–42,44,45]. Eight studies (36.4%) used non-contrast CT images [25,26,28,30–33,43]. Whereas only one study (4.5%) reported use of contrast-enhanced CT images [46] (Table 1).

Use of CT Dose

Ten studies (45.5%) reported tube voltage [25,26,28,30,33,37,39,41,43,46], of them all studies used 120 kVp except one study which used 120–140 kVp [33]. Nine studies (40.1%) reported tube current [25,26,28,30,33,37,39,43,46], of which 2 studies used 11 mA [25,26], two studies 100 mA [28,30], and one study of each used 50 [39], 120 [33], 100–300 [37], 250–300 [43], and 300–500 [46] tube current, respectively.

Use of Software for CT Analysis

Five studies (22.7%) used OsiriX (Pixmeo, Geneva, Switzerland) software [25,26,28,30,43], four studies (18.2%) used Aquarius 3D Workstation (TeraRecon Inc., San Mateo, CA) software [25,26,28,30,43]; three studies (13.6%) Image J (NIH, USA) software [27,44,46]; two studies (9.1%) used SliceOmatic (Tomovision, Montreal, QC, Canada) software [32,33]; one study (4.5%) Interactive Data Language (ITT Visualization Solutions, Boulder, CO, USA) software [35]; one study Carimas (version 2.9, Turku PET Centre, Turku, Finland) software [39]; one study MIPAV 4.1.2 (NIH, USA) software [42]; one study used Eclipse CT ranger tool [29]; and another study used PLANET Onco (DOSIsoft, Cachan, France) software [31],

respectively. In contrast, three study did not report type of software they were used for CT image analysis [34,38,45] (Table 1).

Use of Radiodensity Ranges for CT Analysis

The range of HU values used to quantify adipose tissue radiodensity also varied between studies. Eight studies (36.4%) used HU range −45 to −195 [29,34,36–38,40,41,45]; six studies (27.3%) −30 to -190 [27,31–33,43,44], and two studies (9.1%) used range from -50 to -200 [28,30]. One study (4.5%) used range from −50 to −250 [46]; one study −250 to −50 [25], and another study −300 to −10 [39], respectively. In contrast, three studies (13.6%) did not report radiodensity range [26,35,42] (Table 2).

Table 2. Range and mean HU values for fat radiodensity in studies.

Range	Male		Female		Ref
	VAT radiodensity	SAT radiodensity	VAT radiodensity	SAT radiodensity	
−195 to −45	−95.2 ± 4.5	−99.6 ± 4.5	−92.4±4.4	−102.3±5.1	[34]
−195 to −45	−95.2 ± 4.5	−99.6 ± 4.4	−92.2 ± 4.4	−102.3 ± 5.1	[36]
−195 to −45	−95.5 ± 4.5	−99.8 ± 4.6	−91.9 ± 4.3	−101.9 ± 5.3	[37]
−195 to −45	−95.5 ± 4.5	−99.8 ± 4.8	−92.3 ± 4.4	−102.0 ± 5.9	[38]*
−195 to −45	−93.9 ± 7.0	−106.3 ± 4.3	−93.9 ± 4.7	−100.8 ± 5.2	[40]*
−195 to −45	−95.5 ± 4.5	−99.9 ± 4.5	−92.0 ± 4.3	−101.9 ± 5.5	[41]
−195 to −45	-	−99.2 ± 6.1	-	-	[29]^
−195 to −45	−95.2 ± 4.5	−99.6 ± 4.4	−92.5 ± 4.4	−102.3 ± 5.1	[45]
−190 to −30	−85.9 ± 10.6	−101.8 ± 29.0	−85.9 ± 10.6	−101.8 ± 29.0	[27]#
−190 to −30	−89.6 (−94.7 to −82.1)	−99.7 (−103 to −94.0)	-	-	[43]¥
−190 to −30	-	-	−87.8 ± 7.5	−103.2 ± 5.2	[44]±
−190 to −30	−96.0	−96.0	−89.5	−99.0	[31]
−190 to −30	−85.0 ± 9.0	−93.0 ± 12.0	−85.0 ± 9.0	−93.0 ± 12.0	[32]#
−190 to −30	−91.5 (−94.9 to −82.0)	−87.8 (−94.1 to −72.0)	-94.1 (−98.8 to -87.6)	−96.0 (−101.0 to −83.4)	[33]
−200 to −50	−92.0 (−110 to −63.8)	−96.7 (−114 to −95.1)	-	-	[28]$
−200 to −50	−97.5 (−114 to −66.7)	−101 (−116 to −66.6)	-	-	[30]$
−190 to 50		−95.8 ± 7.7		−95.8 ± 7.7	[46]£
−250 to −50	−89.2 ± 9.8	−98.7 ± 8.2	−89.2 ± 9.8	−98.7 ± 8.2	[25]#
−300 to −10	-	-	−111.9 ± 6.8 (−94.9 ± 12.2)	−112.3 ± 7.1 (−97.7 ± 17.1)	[39]¶

Values are expressed as mean ± SD; *, Baseline measure; ^, Male and SAT radiodensity only; ¥, Male only and reported median with range; ±, Reported female only; #, Did not report male/female separately; $, Reported median with range and did not report male female separately; £, Reported only SAT radiodensity; ¶, Female obese and non-obese (in parenthesis) only.

DISCUSSION

The analysis of body composition has become more precise and consistent with the development of CT based imaging analysis tools [51]. Analysis of body composition to quantify and characterize skeletal muscle and adipose tissue by CT has become more common in clinical research settings, where routine CT images taken as part of diagnostic work up and treatment planning exist in patient record. However, considerable differences between studies existed with respect to the abdominal regions analyzed, use of slice thickness, contrast medium, dose, software and radiodensity ranges to assess adipose tissue radiodensity in humans. In most cases, background or rationale was not provided for one method used over another. These differences may explain the reason for the variation in mean VAT and SAT radiodensity reported in published literature (Table 2). A standardized approach to assessment of adipose tissue radiodensity is required to ensure consistency in reporting in the published literature similar to what has been done for muscle characteristics [48,52].

The concept of adipose tissue radiodensity being prognostic is new and implicated previously in studies primarily focusing metabolic abnormalities [34–44]. Half of the studies (11 out of 22) included in this review focused on metabolic complications and seven of those were carried out by the same research group using offspring and third generation cohort participants of the Framingham Heart Study [34,36–38,40,41,45]. Nine studies (41%) reported within the oncology setting [25–33] where routine CT analysis performed for diagnosis, staging and clinical follow-up in cancer populations and recent studies are showing prognostic significance of adipose tissue radiodensity in cancer survival [20,22].

Lower adipose tissue radiodensity is indicative of higher adipose tissue lipid content [13,14], and associated with weight gain, obesity and cardiometabolic risks [34,37–41,53]. In contrast, higher adipose tissue radiodensity (i.e., adipose tissue depleted of lipid content) is associated with shorted survival in cancer patients [28,30,32,33,54], as well as increase mortality in older adults [45]. Several potential mechanisms have been proposed to explain higher VAT and SAT radiodensity, such as increased vascularity [15,55], and/or deposition of extracellular matrix or fibrosis [35,45,56]. Tissues with higher vascularity appear to have higher radiodensity due to the increased blood content [55]. For example, brown adipose tissue shows higher radiodensity due to having higher vascularity [15]. Higher radiodensity of adipose tissue is associated with smaller adipocytes and increased extracellular matrix deposition (fibrosis) in primates [35]. A recent study also indicated that higher subcutaneous adipose tissue radiodensity is associated with reduced subcutaneous and visceral adipose tissue as well as reduced leptin levels [33]. Fibrosis is attributed to excessive deposition of extracellular matrix (ECM) protein components and subsequent interstitial deposition of fibrotic material [16]. Higher radiodensity has been observed in fibrotic plaques compared to

lipid-rich plaques in a study of coronary artery plaques [56]. There was a positive association between higher adipose tissue radiodensity and elevated urinary connective tissue growth factor, a marker of systemic fibrosis [45]. The literature therefore would suggest that having adipose tissue with high radiodensity is pathological [45], or at the very least reflects a change from the normal metabolism of adipose tissue [15,35,45]. The high attenuation of adipose tissue is thus thought to reflect the changes of adipocytes and adipose microenvironment [25,35].

There is substantial variation of abdominal region selected for analysis on adipose tissue radiodensity measurements. Although L4–L5 is a commonly used landmark for measuring VAT and SAT volume [57,58], several studies have shown that a single image in the upper abdomen (i.e., at L1–L2 or L2–L3) is a more suitable surrogate for total VAT [59–61], and SAT volume [59] than an image at L4–L5. However, L3 is the most frequently reported region of interest, since it has been shown that the body cross sectional areas at L3 is linearly correlated to total adipose tissue [54], VAT and SAT [62], as well as whole body muscle mass [54]. Reviewed studies used L3 (4 studies) [31–33,46], L4 (4 studies) [26–28,30], and L4/L5 regions (4 studies) [29,35,43,44]. Therefore, it would seem important to determine a representative region for adipose tissue radiodensity measurement and form a consensus among researchers to apply the defined region in future studies. L3 has been validated against whole body for muscle and adipose tissue content, and this vertebral level enables definition of a landmark to make the comparisons between studies or to evaluate changes over time [54,63].

The slice thickness is another variable parameter in CT image analysis and ranged from 0.625 mm [39] to 10 mm [35]. Thinner slices provide better detail and spatial resolution; conversely, the noise in the CT image decreases with thicker slice [64]. A recent study showed that, compared to 2mm slice, both total adipose tissue index and mean attenuation increased on slices with a thickness of 10 mm [65]. The effect of increased slice thickness on mean adipose tissue attenuation was recently confirmed in a study that compared 2- and 5 mm thick slices [66]. Mean attenuation was lower in thinner slices for each of the adipose tissue depots ranging from a mean difference of −1.0% for SAT and −2.4% for VAT [66]. Slice thickness is also important to minimize partial volume artifacts. A thicker slice has a greater chance of containing a mixture of tissues than a thinner slice. The use of thick slices increases the probability of mixing fat tissues with nearby extra-fat soft tissues [67], and thereby misestimating the actual attenuation. For example, increasing slice thickness size by 50% can yield a decrease in the standardized uptake values by 7% [67]. By using thin slice sections partial volume artifacts can be avoided. Similarly, to limit image noise, adding several thin sections or by using multi-slice CT (MSCT) a thicker section can be generated (section reconstructions). The MSCT has several advantages over single slice CT [68–70]. MSCT provides better diagnostic ability by not only reducing time, but also reducing radiation.

The quality of image also improved. It has been shown that during weight loss, changes in VAT and SAT are poorly evaluated on single slice imaging [71], while good results for intra-abdominal fat obtained by multi-slice imaging [72]. Therefore, use of single or MSCT will have effect on adipose tissue radiodensity measurement, although only few (6 out of 22) of our selected studies used or reported MSCT.

There was substantial variability in the range of HU values applied to adipose tissue (Figure 2). The HU range used to quantify adipose tissue in from the studies reviewed ranged within +50 to −300 HU. 36.4% of studies reviewed used ranges from −190 to −45, while one study [46] used range from +50 to −190 to define adipose tissue radiodensity. HU ranges −150 to −50 for VAT and −190 to −30 for SAT are recommended for optimal measurement [73,74].

Contrast agents can also affect radiodensity results. Administering contrast media (i.e., iodine) leads to higher radiation absorption and therefore higher radiodensity, especially in soft adipose tissues. In the case of skeletal muscle and bone, intravenous contrast administration results in significantly increased mean radiodensity measures when compared with unenhanced images [75]. Thus, contrast enhanced images reduce attenuation values compared to non-contrast tissues. This was confirmed in a recent study in which adipose tissue index decreased by ≥6.5% after contrast media was administered [65]. The overall VAT attenuation also changed from −90 to −87 HU after contrast enhancement [65]. Moreover, there is evidence to suggest that muscle radiodensity in men and women is affected differently by intravenous contrast administration [76]. The type and timing of contrast agent may affect CT fat radiodensity measures, although this remains unclear. Therefore, contrast enhanced CT image analysis for adipose tissue should be avoided in prospective clinical studies. The majority of studies reviewed (59.1%) did not report whether contrast was used in the analysis [27,29,34–42,44,45,53], while only one study reported using contrast enhanced CT analysis [46]. Authors must report the use of contrast enhanced CT image analysis particularly in evaluating longitudinal changes in clinical cohorts, and to be aware of their effect when comparing results between different cohorts.

In clinical practice different CT doses are used by different institutions and there is no standard protocol for efficient use of CT dose to patients in clinical settings. In our review, we found that most studies (55%) did not report what type of dose they used. Moreover, studies those reported doses differ largely in terms of use of tube current (11 mA to 500 mA). Radiation exposure during medical imaging (mostly from CT imaging) has significant impact on cancer risk and it is reported that exposure to ionizing radiation might be responsible for 0.6–3.2% of malignant tumors in developed countries [77]. Since tube voltage and or tube current is easier to modify and the result is more predictable, lowering tube current or tube voltage can be the most direct way of achieving radiation dose reduction. However, reduced-dose CT images have a higher noise level than standard-dose CT

images and image noise is inversely proportional to the square root of the radiation dose [78]. Therefore, a standard method and technique for radiation dose reduction should be developed to ensure that radiation exposure is kept as low as possible without affecting quality of CT scan.

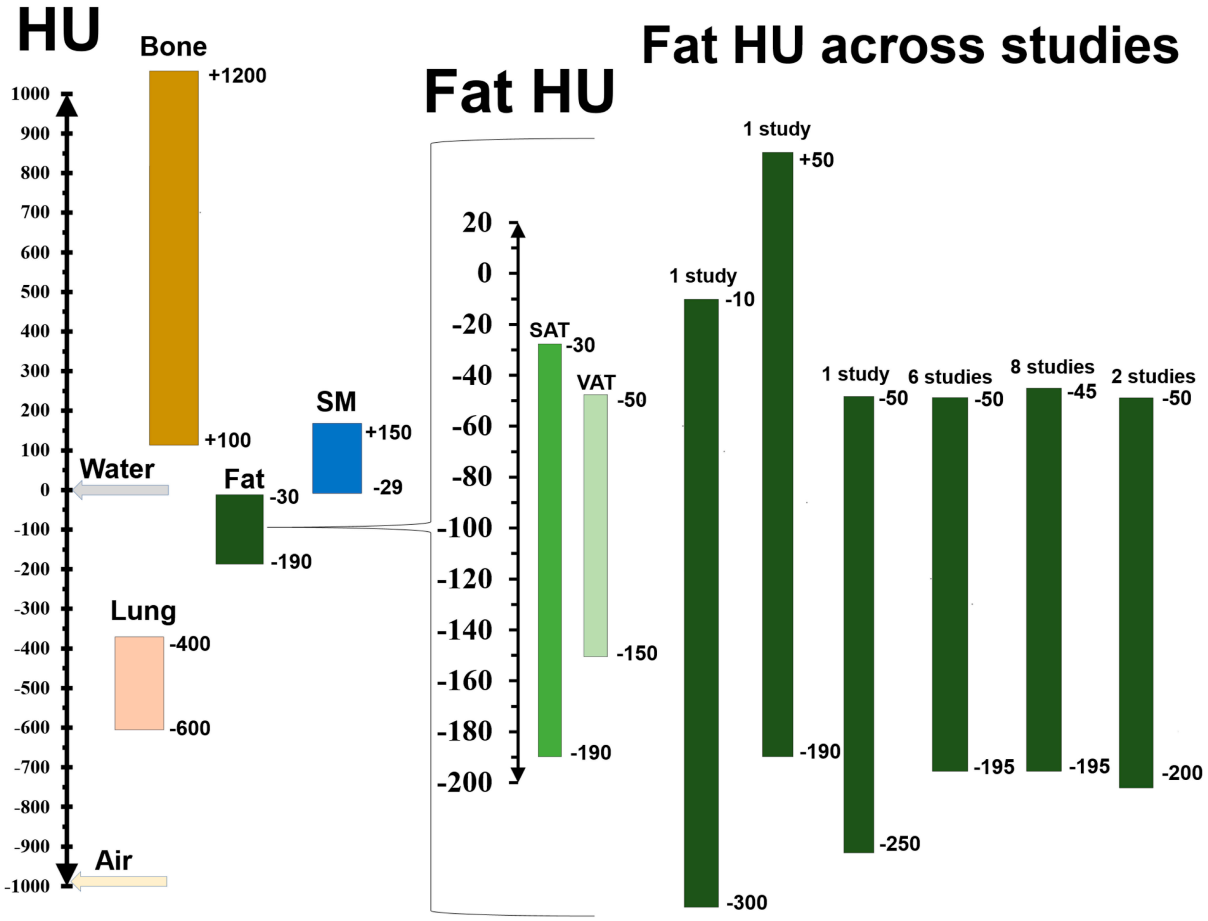

Figure 2. Hounsfield scale values for tissues (left panel), standard HU range for VAT and SAT (middle panel), and variation of use of adipose tissue radiodensity range across studies (right panel). Abbreviations: HU, Hounsfield unit; SM, skeletal muscle; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Use of different software packages to analyze the CT images impacts the analysis. A variety of software packages for CT images analysis were used in the reviewed literature. In a recent study Rollins et al. [79] compared two commonly used software packages OsiriX (v7.5.1, Pixmeo, Bernex, Switzerland) and SliceOmatic (v5.0, TomoVision, Montreal, Canada), for different body composition parameters including adipose tissue and skeletal muscle. They showed that skeletal muscle measure was significantly higher, whereas adipose tissue was significantly lower when the analyses were performed with OsiriX compared with SliceOmatic. The clinical relevance of these statistically significant differences between different software packages is not known and need to be tested in future studies.

From the reviewed literature, it seems clear that VAT and SAT radiodensity values are distinct between male and female (Figure 3). The mean range of VAT radiodensity reported in the literature was −85.0 HU to −97.5 HU for males and −85.0 HU to −111.9 HU for females; while reported mean range SAT radiodensity was −87.8 HU to −106.3 HU for males and −93.0 HU to −112.3 HU for females, respectively (Table 2). This difference might be due to use of different methodologies across studies. However, there are substantial sex differences in adipose tissue in humans. Generally, females have a higher percentage of body fat compared to males [80]. Fat distribution also differs between sexes; females have greater fat accumulation in the gluteal–femoral region and higher SAT volume compared to men, whereas men store more fat in the abdominal region (VAT) [23]. Sex differences in adipose tissue distribution and correlations to metabolic health are well established [81,82]; while in cancer patients, subcutaneous and visceral adiposity also differs between sexes [20].

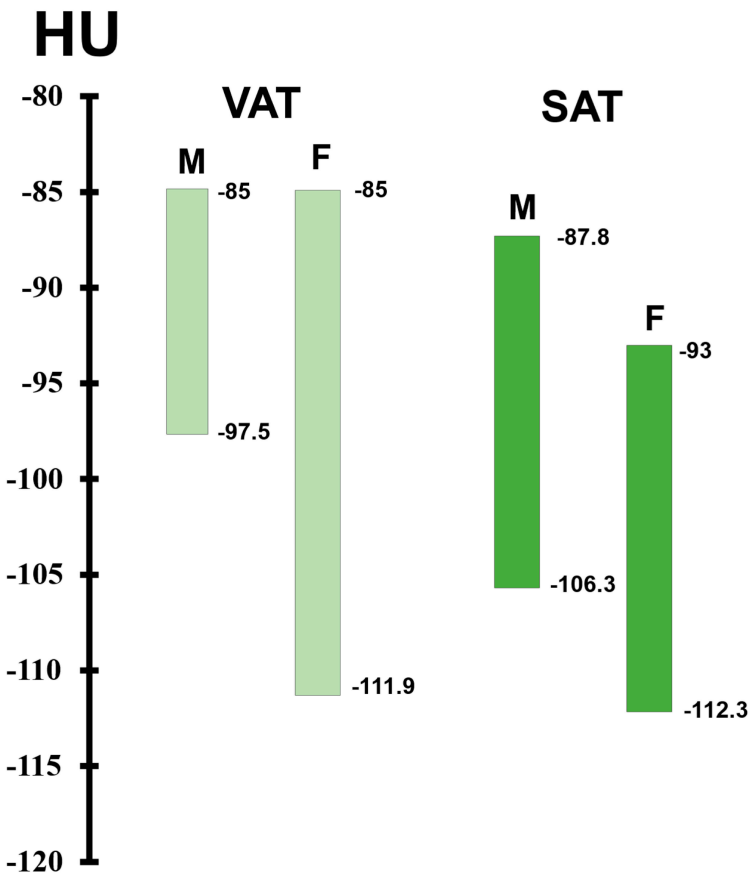

Figure 3. Variation of VAT and SAT radiodensity (mean range) in male and female across studies. Abbreviations: F, female; HU, Hounsfield unit; M, male; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Another possible cause of inaccurate adipose tissue radiodensity measurement is the presence of edema which can be observed in

bedridden hospitalized patients. A recent study reported that people with ascites show lower intraclass correlation coefficient for quantification of visceral fat among the various measurement methods [83]. They suggest that edematous changes in intraabdominal organs and ascites make it harder to discriminate fat from other soft tissue and might increase fat attenuation [83]. However, to our best knowledge, no study reported the effect of edema on the quantification of adipose tissue radiodensity.

CONCLUSIONS

This review indicates substantial methodological variability in available literature evaluating VAT and SAT radiodensities. Many studies do not report the details of CT analysis methodology, such as abdominal region used, thickness of slice, whether contrast media used or not, use of software, or radiodensity range used to define VAT and SAT. This might be due to lack of knowledge of the effect of different CT acquisition parameters on body composition segmentation. Application of a variety of protocols to determine adipose tissue radiodensity limits the potential to apply this measure of body composition in prediction of clinical outcomes at this time. Consistent use and reporting of these methodologies will help comparing results between different studies.

AUTHOR CONTRIBUTIONS

MM was involved in compilation of data and writing of manuscript. LM, CS and VCM assisted with revising the manuscript. All authors have commented on the manuscript and approved the final version.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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