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Original article

Computed tomography reference values for visceral obesity and increased metabolic risk in a Caucasian cohort

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SUMMARY

Background: Visceral obesity is associated with the metabolic syndrome. The metabolic risk differs per ethnicity, but reference values for visceral obesity for body composition analyses using Computed Tomography (CT) scans in the Caucasian population are lacking. Therefore, the aim of this study was to define gender specific reference values for visceral obesity in a Caucasian cohort based upon the association between the amount of visceral adipose tissue (VAT) and markers of increased metabolic risk.
Methods: Visceral Adipose Tissue Area Index (VATI cm^2/m^2) at the level of vertebra L3 was analyzed using CT scans of 416 healthy living kidney donor candidates. The use of antihypertensive drugs and/or statins was used as an indicator for increased metabolic risk. Gender specific cut-off values for VATI with a sensitivity $\geq$80% were calculated using receiver operating characteristic (ROC) curves.
Results: In both men and women who used antihypertensive drugs, statins or both, VATI was higher than in those who did not use these drugs ($p \leq 0.013$). In males and females respectively, a value of VATI of $\geq$38.7 cm^2/m^2 and $\geq$24.9 cm^2/m^2 was associated with increased metabolic risk with a sensitivity of 80%. ROC analysis showed that VATI was a better predictor of increased metabolic risk than BMI (area under ROC curve (AUC) = 0.702 vs AUC = 0.556 in males and AUC = 0.757 vs AUC = 0.630 in females).
Conclusion: Gender and ethnicity specific cut-off values for visceral obesity are important in body composition research, although further validation is needed. This study also showed that quantification of VATI is a better predictor for metabolic risk than BMI.
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1. Introduction

Obesity is an increasing global healthcare problem. It is the number one risk factor for morbidity and mortality in high income countries [1,2]. The estimation is that the number of people with obesity will increase and that in 2030 20% of the worldwide adult population will be obese and another 38% of the population will have overweight [3].

The most dangerous is a high amount of Visceral Adipose Tissue (VAT), also known as abdominal obesity or visceral obesity [1,4]. Visceral obesity is associated with a three times higher risk for developing cardiovascular disease and a five times higher risk for developing diabetes [5–8]. In contrast to subcutaneous adipose tissue, VAT is metabolic active tissue and associated with dyslipidaemia, insulin resistance and hypertension [5,9,10]. Visceral adipose tissue is associated with the development of the metabolic syndrome that consists of a cluster of symptoms that include

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hypertension, impaired glucose metabolism with insulin resistance and dyslipidaemia in the presence of obesity [5,6,11,12].

VAT can be measured using Computed Tomography (CT) scans. On CT scans every tissue has its own tissue specific shade of gray, which is measured in Hounsfield Units (HU). Using predefined HU ranges, visceral adipose tissue can be distinguished from other tissues [13]. This method of body composition analysis is a reliable method and increasing in popularity.

Body composition is both gender and ethnicity dependent [14–16]. There are several Asian publications that have reported cut-off values to indicate when VAT actually becomes a metabolic risk factor [17–22]. However, it is also known that with the same BMI Asians have a higher morbidity and mortality risk compared to Caucasians [16,23]. Therefore these cut-off values may not be applicable for a Caucasian cohort. Hence, there is need for reference values in a Caucasian population that identifies a pathological threshold beyond which the amount of visceral adipose tissue becomes associated with metabolic complications.

In body composition research it is important to use general applicable reference values. This is recently shown in a cohort of Intensive Care patients where sarcopenia, defined by reference values obtained from a representative, otherwise healthy cohort, was able to point out patients at risk for dying in the hospital [24]. Likewise, when studying the effect of body composition on disease related outcomes in specific populations, it may be crucial to use cut-off values for pathological visceral obesity within these specific populations.

Therefore, the aim of this study was to assess the association between visceral adipose tissue and metabolic risk in a Caucasian cohort and to define gender specific reference values for visceral obesity based upon this association.

2. Methods

2.1. Study population

The study cohort consisted of individuals that were screened for potential living kidney donation in the Amsterdam University Medical Center between 2006 and 2014. Individuals were included in this study if they were medically approved as a kidney donor candidate [25], had a Caucasian background, and a non-contrast CT-scan available to perform body composition analysis. Demographics and data regarding BMI, use of medication and comorbidities were retrieved from the medical record of the individuals as part of the kidney donor screening. Data from this cohort were published before by van der Werf et al. [25].

2.2. Measurement of Visceral Adipose Tissue Index (VATI)

CT-scan analysis of body composition was performed according to established methods as described by Mourtzakis et al. [13]. Briefly, a single slice of each individual CT scan was selected at the level of the 3rd lumbar vertebra. Thereafter, using tissue specific Hounsfield Unit (HU) ranges, the total cross-sectional area (cm^2) of visceral adipose tissue (VAT) (−150 to −50 HU) was determined. The total area of VAT is estimated by assessing the total tissue area in cm^2 at the level of vertebra L3 and dividing it by height in meter squared. This results in the L3 Visceral Adipose Tissue Index (VATI) given in cm^2/m^2 [13]. CT scans were reviewed for sufficient quality for analysis, including no artifacts and clear differentiation between visceral adipose tissue and the surrounding tissues. CT scans were analyzed using SliceOmatic V5.0 (TomoVision, Magog, Canada) software for Microsoft Windows®.

2.3. Assessment of metabolic risk

The metabolic syndrome is defined as: central obesity measured as ethnic specific waist circumference, plus any of two of the following: triglycerides >1.7 mmol/L or on specific treatment, high-density lipoprotein cholesterol <1.03 mmol/L in males and <1.29 mmol/L in females or on specific treatment, blood pressure ≥130/85 mmHg or on anti-hypertensive treatment and/or fasting plasma glucose ≥5.6 mmol/L or previously diagnosed with type 2 diabetes [14].

In the present study, as an indicator of complications that may be associated with the metabolic syndrome, the use of antihypertensive drugs and/or statins was used as an indicator for increased metabolic risk.

In this cohort of living kidney donor candidates, individuals with diabetes were excluded as kidney donor and could therefore not be included in the analysis [25].

2.4. Reference values for visceral obesity

To establish reference values for visceral obesity, receiver operating characteristic (ROC) analysis was performed using the presence or absence of increased metabolic risk (yes/no) based on medication use as outcome and VATI as discrimination threshold. A cut-off value of VATI with a sensitivity of at least 80% was considered to be relevant.

To compare the applicability of VATI with Body Mass Index (BMI), additional ROC analysis was performed using BMI as discrimination threshold. The area under the curve of the ROC analysis (AUC) was used as measure for overall prediction quality.

2.5. Statistical analysis

Categorical variables are presented as number of patients (%), where mean ± standard deviation (SD) is used for numerical variables. Numerical variables were checked for normality using histograms.

Independent-samples t-tests were used to assess the relationship between VATI and the use of statins and/or antihypertensive medication. Mann–Whitney U-tests were used as sensitivity analyses.

Since body composition is gender dependent, statistical analysis for VATI for men and women was performed separately [15].

Analyses were performed using IBM SPSS Statistics for Windows version 25 (Armonk, NY, USA; IBM Corp.) and Prism version 8.0.0 (GraphPad Software, San Diego, CA, USA). A p-value ≤0.05 was considered statistically significant. The statistical analyses were supervised by a statistician (BW).

2.6. Ethics

The study protocol was reviewed and approved by the Medical Ethics Committee of the VUmc. The Medical Research Involving Human Subjects Act does not apply to the study and the study was conducted in accordance with the Declaration of Helsinki.

3. Results

3.1. Study population

Between 2006 and 2014, 692 individuals were selected as potential living kidney donor candidate of whom 639 were eligible as kidney donor. Of these 639 individuals, 223 individuals were

excluded from this study because there was no CT scan available or the CT scan was of insufficient quality. This resulted in 416 individuals (173 men (42%) and 243 women (58%)) eligible for analysis. The flowchart of the inclusion and exclusion of individuals is presented in Fig. 1.

Mean (±SD) age of the subjects was 52.5 (±11.8) years. Mean (±SD) BMI was 25.8 (±3.5) kg/m^2, 48 persons (12%; 21 males, 27 females) of the studied cohort used antihypertensive drugs, and 21 persons (5%; 6 males, 15 females) used statins. The characteristics of the study cohort are presented in Table 1. The Visceral Adipose Tissue Index per BMI group (<24.9, 25.0–29.9 and >30) and per gender is given in Table 2.

3.2. The association between VATI and metabolic risk

Mean VATI was significantly higher in males and females who use antihypertensive drugs compared to individuals who did not use antihypertensive drugs (Table 3). Mean VATI was also significantly higher in individuals who were using statins compared to individuals who did not use statins (Table 3). In keeping, mean VATI was significantly higher in subjects with an increased metabolic risk, defined as the use of either statins and/or antihypertensive medication, compared to subjects who did not use medication for hypertension and/or hypercholesterolemia (Fig. 2, Table 3).

3.3. Reference values for visceral obesity

There were 23 males who used medication for hypertension and/or statins. For males the area under the ROC curve (AUC) was 0.702 with a 95% confidence interval (CI) of 0.580–0.823 ($p = 0.002$). To determine a cut-off value for visceral adipose tissue, the first VATI value was chosen where a sensitivity value of at least 80% was reached. In males this resulted in a sensitivity of 82.6% (specificity 42.7%) and the value of VATI that indicated an increased risk was 38.71 cm^2/m^2.

There were 37 females who used medication for hypertension and/or statins. In this group, the area under the curve (AUC) was 0.757 with a 95% confidence interval (CI) of 0.676–0.838 ($p < 0.001$). In females, the first value where a sensitivity of at least 80% was reached was 81.1% (specificity 61.2%) and the value of VATI that indicated an increased risk was 24.94 cm^2/m^2.

VATI was a better predictor for the increased metabolic risk (AUC) than BMI for both males and females as shown in Fig. 3. In males, the AUC was 0.556 (95% CI 0.418–0.695, $p = 0.385$) and in females the AUC was 0.630 (95% CI 0.531–0.729, $p = 0.012$) for BMI.

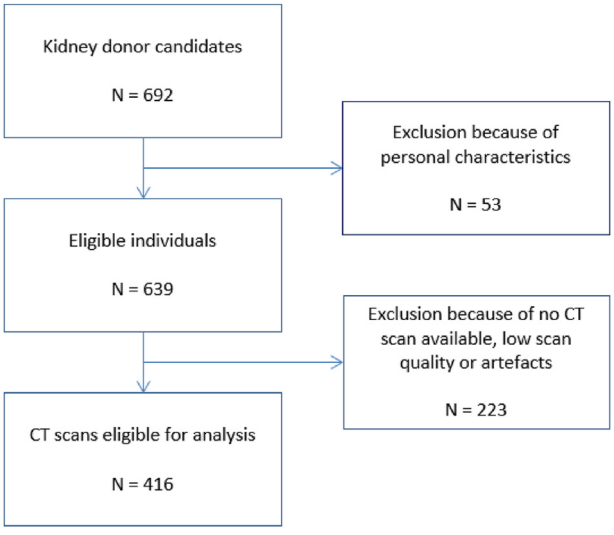

Fig. 1. Flowchart of the inclusion and exclusion.

Table 1
Characteristics of the study cohort.

		Male (N = 173)		Female (N = 243)	
		Mean or number	SD or %	Mean or number	SD or %
Demographics	Age (years)	51.0	±12.4	53.5	±11.3
Body composition	Weight (kg)	86.0	±12.2	72.0	±11.1
	Height (cm)	181.5	±7.7	168.1	±6.4
	BMI (kg/m^2)	26.1	±3.3	25.5	±3.7
Medication use	Antihypertensive drugs[a]	21	12.1%	27	11.1%
	Statins[a]	6	3.5%	15	6.2%

Data are presented as absolute number (%) or mean ± SD.
[a] Medication use is retrieved from the medical records of individuals.

Table 2
Gender specific Visceral Adipose Tissue Index per BMI group.

Visceral Adipose Tissue Index (cm^2/m^2)				
	BMI < 24.9	BMI 25.0–29.9	BMI > 30.0	Total
Male	30.8 ± 17.2 (N = 64)	49.7 ± 20.4 (N = 86)	72.2 ± 22.4 (N = 23)	45.7 ± 23.7 (N = 173)
Female	16.2 ± 12.0 (N = 118)	33.1 ± 16.3 (N = 95)	51.6 ± 23.1 (N = 28)	26.9 ± 19.4 (N = 241[a])
Total	21.3 ± 15.6 (N = 182)	41.0 ± 20.1 (N = 181)	60.9 ± 24.9 (N = 51)	34.7 ± 23.2 (N = 414[a])

Visceral Adipose Tissue Index parameters at baseline measured on a Computed Tomography scan at the level of vertebra L3. The values were corrected for the height of individuals resulting in a L3-index given in cm^2/m^2. Values were given per gender and per Body Mass Index (BMI) measured in kg/m^2. Data are presented as mean (±SD).
[a] For two females BMI was missing.

4. Discussion

This study was designed to assess the association between the amount of visceral adipose tissue and indicators of metabolic risk and to define gender specific reference values for visceral obesity upon this association in a Caucasian cohort. The use of antihypertensive drugs and/or statins was used as an indicator for increased metabolic risk. In an otherwise healthy Caucasian cohort, a value of VATI of ≥38.7 cm^2/m^2 for males and ≥24.9 cm^2/m^2 for females was associated with an increased metabolic risk with a sensitivity >80%. Also, VATI showed to be a better predictor for metabolic risk than BMI for both genders.

Given the growing prevalence of obesity and the metabolic syndrome and the increasing scientific attention for these problems reference values for visceral obesity are needed. The importance of generally applicable reference values in body composition research is recently shown in previous research [24,25]. Several studies have been performed addressing the association between the amount of VATI and clinical outcome. In all of these studies, cut-off values were based upon the investigated study cohort or upon disease outcome [4,26–31]. When studying the effect of visceral obesity on disease related outcomes in specific cohorts it may be crucial to define pathological visceral obesity using externally validated reference values [24]. To define a reference value for visceral obesity for body composition analysis using CT scans it is important to identify those patients for whom the amount of visceral adipose tissue actually becomes a health risk.

To our knowledge, this is the first study providing reference values for visceral obesity for body composition analysis using Computed Tomography scans in a relatively homogenous Caucasian

Table 3
Visceral Adipose Tissue Index and indicators for metabolic risk.

Visceral Adipose Tissue Index (cm^2/m^2)									
	Antihypertensive drugs+	Antihypertensive drugs−	*p*-value	Statins+	Statins−	*p*-value	Antihypertensive drugs+ and/or statins+	Antihypertensive drugs and statins−	*p*-value
Male	43.1 ± 21.8 (N = 21)	64.2 ± 28.9 (N = 152)	0.004	69.1 ± 26.0 (N = 6)	44.8 ± 23.2 (N = 167)	0.013	62.8 ± 28.1 (N = 23)	43.1 ± 21.9 (N = 150)	<0.001
Female	24.8 ± 17.6 (N = 27)	43.9 ± 24.4 (N = 216)	<0.001	41.0 ± 15.9 (N = 15)	26.0 ± 19.3 (N = 228)	0.003	42.4 ± 22.4 (N = 37)	24.1 ± 17.4 (N = 206)	<0.001

Indicators of metabolic risk (the use of antihypertensive drugs and/or statins) and Visceral Adipose Tissue Index parameters at baseline measured on a Computed Tomography scan at the level of vertebra L3. The Visceral Adipose Tissue area was corrected for height resulting in a L3-index given in cm^2/m^2. Values were given per gender as mean (±SD). Mann–Whitney U-tests were used as sensitivity analyses and showed similar *p*-values yielding the same conclusions.

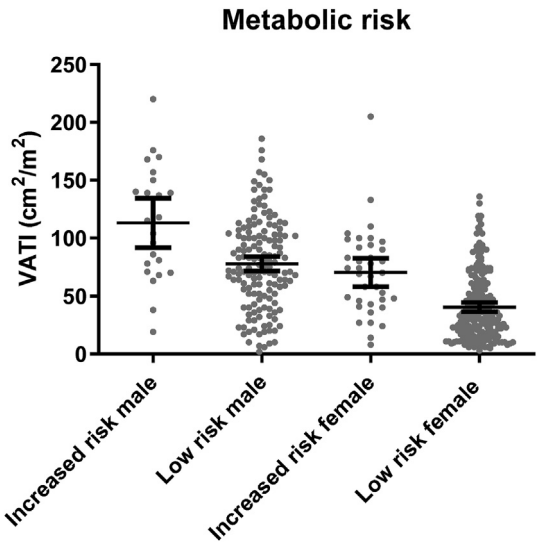

Fig. 2. Mean Visceral Adipose Tissue Index and metabolic risk per gender. Increased metabolic risk is defined as: the use of antihypertensive drugs and/or statins. Low metabolic risk is defined as: no use of antihypertensive drugs or statins. Data are presented with mean (95% confidence interval). Visceral Adipose Tissue Index (VATI) measured at the level of L3 on an abdominal CT-scan and indexed for height and is given in cm^2/m^2.

cohort. In the Asian population, several publications have reported cut-off values to indicate when visceral obesity becomes a risk factor [17–22]. However, body composition is ethnicity dependent and with the same BMI Asians have a higher morbidity and mortality compared to Caucasians [14,16,23]. Therefore these reference values may not be applicable in the Caucasian population.

In Asian studies, cut-off values on Computed Tomography of VAT that are associated with the metabolic syndrome approximate 133–136 cm^2 in men and 91–95 cm^2 in women [20,32,33]. Commonly, tissue areas measured at a single CT slice are normalized to height, but unfortunately no normalized ratios are reported in the Asian literature. Accounting for an average height of 1.53 and 1.74 m for Japanese and Korean males respectively and 1.53 and 1.61 m for Japanese and Korean females respectively, it can be estimated that the cut-off value form visceral obesity based on normalized VATI based on Asian data approximates 44–58 cm^2/m^2 for males and 35–41 cm^2/m^2 for females. These reference values are higher than the reference values found in the current study. However, the present study consists of a cohort of relatively healthy living kidney donor candidates and in the Asian studies also patients from obesity clinics were included [34]. Besides, some studies used CT slices from the umbilical level with wider Hounsfield Unit ranges for adipose tissues (HU −250 to −50) [20,32].

Body composition and also the amount of visceral adipose tissue is different between men and women [15]. Therefore gender specific reference values were created. In the present study, it appears that even when the amount of VAT is corrected for height, the relative amount of VATI that is associated with health problems is much lower in women than in men. The average normalized VATI in women with an increased metabolic risk was the same as in men without increased metabolic risk (Fig. 2). This may suggest that women with a masculine fat

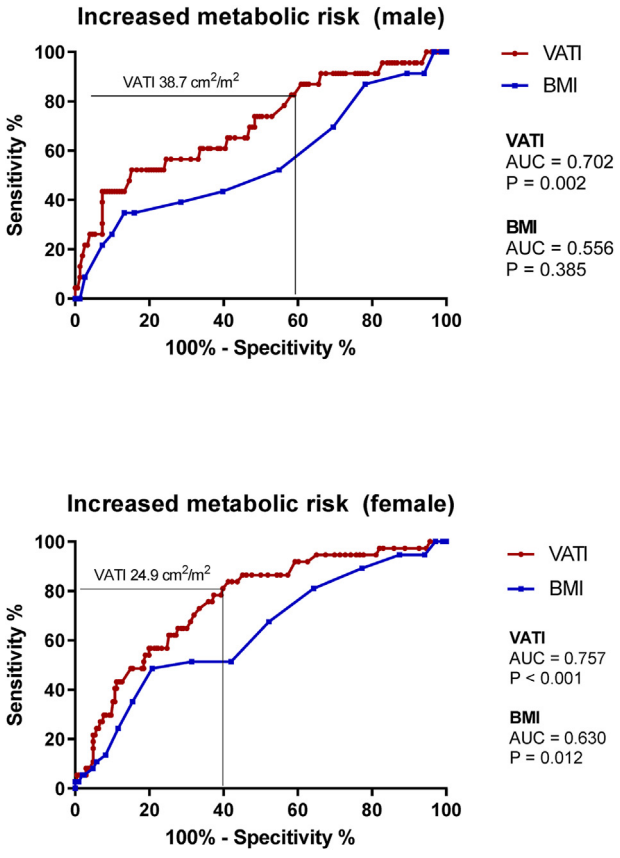

Fig. 3. Reference values for visceral obesity per gender. Increased metabolic risk is defined as: the use of antihypertensive drugs and/or statins. The risk is given per gender using Receiver Operating Characteristic (ROC) analysis. Visceral Adipose Tissue Index (VATI) measured at the level of vertebra L3 on an abdominal CT-scan is given in cm^2/m^2. Body Mass Index (BMI) is given in kg/m^2. The value with a sensitivity of at least 80% is used as a cut-off value for visceral obesity indicating increased metabolic risk. VATI showed to be a predictor with a higher sensitivity and specificity for metabolic risk than BMI.

distribution with more VAT around the waist run a higher risk of developing the metabolic syndrome.

Using ROC analysis the current study also showed that the amount of visceral adipose tissue on Computed Tomography seemed to be a better predictor for metabolic risk than BMI. This is in agreement with previous studies, where the amount of visceral adipose tissue was a better predictor for the development of the metabolic syndrome compared to BMI [1,4,20,33,35]. Previous research also showed that the amount of VAT is a better indicator for the risk on the metabolic syndrome than waist circumference [20,33]. Both BMI and waist circumference contain both subcutaneous adipose tissue and visceral adipose tissue. However, it is the amount of visceral adipose tissue that causes the highest risk on the metabolic syndrome and associated health problems since visceral adipose tissue is metabolically active [5,10].

This study has several strengths and weaknesses. Strong point of the study is that a large and relatively homogenous cohort of healthy kidney donor candidates was used. Body composition measurements using Computed Tomography is an accurate and widely used method with a good reproducibility [13,36]. For the measurement of visceral adipose tissue and therefore visceral obesity, CT and MRI are the golden standards since visceral adipose tissue can be easily distinguished from other tissues [4,32,37–39]. However, the visibility of VAT is also dependent of the anatomy of the intra-abdominal organs. The movement of soft tissues, bowel movement and the variable filling of the intestine can cause variability in the measurements [4]. However, VAT measurements at 5 cm superior to the L4–L5 level showed a high correlation with total adipose tissue [4,40]. A limitation of the study is that we only could use prescribed medication as readout of increased metabolic risk instead of measured values. In addition, apart from hypertension and dyslipidaemia, hyperglycaemia and diabetes are characteristics of the metabolic syndrome. Since diabetes and hyperglycaemia are contra-indications for kidney donation subjects with these conditions were not present in our cohort. The reference values we propose have a high sensitivity but relatively poor specificity, this is obviously due to the multifactorial pathogenesis of hypertension and dyslipidaemia. Since this is the first study of its kind, external validation of our data is required.

5. Conclusion

In conclusion, VATI value of $\geq$38.7 cm^2/m^2 for males and $\geq$24.9 cm^2/m^2 for females can be used as a reference values for visceral obesity on computed tomography scans. These values of visceral adipose tissue are associated with increased metabolic risk, but further validation is needed. This study also showed that visceral adipose tissue is a better predictor for metabolic risk than BMI for both genders.

Since the amount of visceral adipose tissue and increased metabolic risk is different between men and women, and also different from other populations, it is important to use gender and ethnicity specific reference values to define pathological visceral obesity in body composition research to increase the comparability and reproducibility.

Author statement

Michelle R Baggerman: conceptualization, investigation, analysis, writing – original draft, visualization. **Ingeborg M Dekker**: investigation, writing – review & editing. **Bjorn Winkens**: analysis, writing – review & editing. **Steven WM Olde Damink**: writing – review & editing. **Peter JM Weijs**: conceptualization, resources, writing – review & editing. **Marcel CG van de Poll**: conceptualization, analysis, writing – review & editing, resources, supervision.

Declaration of competing interest

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