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Normal pancreatic volume in adults is influenced by visceral fat, vertebral body width and age

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Abstract

Objectives: The aim was to describe the pancreatic volume (PV) in a cohort of subjects with no prior history of pancreatic disease, and to explore the relationship between PV and conventional two-point measurements of the pancreas. Associations between PV, gender, age, abdominal body composition, and human height were explored as well.

Methods: CT scans from 204 trauma patients (20–80 years, 100 males) were evaluated. PV was measured with semi-automatic segmentation. Standardized two-point measurements of the pancreas were obtained together with L1 vertebral body size (a proxy for human height) and abdominal body composition. Associations between PV and the other parameters were explored using uni- and multivariate linear regression.

Results: The mean PV was 77.9 ± 21.7(SD) cm^3 with an interindividual variability from 18.8 to 139.8 cm^3. The transversal diameter of the pancreatic head showed the strongest correlation to PV ($r = 0.500$, $p < 0.001$). Age, width of the L1 vertebral body, and visceral fat cross-sectional area were all independently associated with PV (all $p < 0.001$), while no independent association was seen for gender ($p = 0.441$).

Conclusions: The pancreatic volume is subject to a large interindividual variability and is associated with age, human height and body composition, while gender had no independent influence on the pancreatic volume. Thus, future studies using PV as an outcome parameter should be evaluated in the context of anthropometric profiles.

Key words: Pancreatic volume—Segmentation—Computed tomography—Body composition—Age—Gender

A change in pancreatic volume (PV) is a hallmark finding of many pancreatic diseases and depending on the disease process and stage, the PV may be affected to different degrees. For example, in patients with chronic pancreatitis (CP) [1] and diabetes [2–5], PV diminishes as the disease evolves; whereas autoimmune and acute pancreatitis [6] and neoplasia [7, 8] may lead to pancreatic enlargement.

Computed tomography (CT) is the typical first-line examination of suspected pancreatic disease. It provides information on tissue morphology and is a quick and reliable non-invasive imaging modality. The simplest method for assessment of pancreatic size on CT is two-point measurements (e.g., antero-posterior (AP) measurement of the body or head). Measuring the exact volume (by outlining the margin of the pancreas on all slices) is more accurate, but additionally more time-consuming.

In chronic pancreatitis, volume reduction is typically associated with a history of repeated acute pancreatitis with ensuing chronic inflammation leading to atrophy. In a previous study, the difference in mean volume between patients with manifest CP and healthy controls was

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found to be 17.3 cm^3 [1]. Previous studies demonstrate large variation in mean volume ranging from 40.4 [9] to 98.8 cm^3 [10] depending on the study [9–16]. Furthermore, the different studies comprise a large interindividual variation in PV among healthy controls from 22.4 to 136.6 cm^3 [13]. This clearly highlights the need for narrower normal reference values to differentiate between a healthy and a pathological pancreatic volume.

Some of the large variation in pancreatic size may be explained by differences in body composition and demographic parameters between subjects. Accordingly, various anthropometric and body composition parameters have been shown to correlate with the size of the pancreas. These parameters include age [11], gender [14], BMI [13], body surface area [3], height [17], and visceral fat mass [16]. However, the previously shown associations are different between studies, with a negative association between age and PV being the only consistent finding [11, 14]. Given the key role of PV as a marker of disease stage and process, it is important to investigate which factors affect the pancreatic size and how these factors interact. This can be done with more advanced analytic methods, taking all parameters into consideration.

We hypothesized that the PV would be associated with body composition and height in addition to the well-established association previously observed between PV and age. In a large cohort of subjects with no prior history of pancreatic or gastroenterological diseases, the aims of the study were: (1) To determine the volume of the normal pancreas using a semi-automatic CT segmentation software in different age and gender groups, (2) to explore the degree of correlation between simple two-point measurements and PV, and (3) to investigate how PV is associated with demographic and anthropometric parameters as well as abdominal body composition measured using CT segmentation.

Materials and methods

This was a retrospective study conducted at Department of Radiology at Aalborg University Hospital. The study was registered at the Danish Data Protection Agency (2017-117).

Study population and eligibility criteria

Two hundred and forty subjects were randomly selected among all patients (n = 892) admitted to Aalborg University Hospital due to trauma in the period from January 2014 to December 2015. To ensure an equally balanced study cohort with respect to age and gender, the selection procedure was stratified by age (by decade) and gender—see flowchart in Fig. 1. The study population was assumed to represent the general population in the best possible way as the CT scan was not undertaken

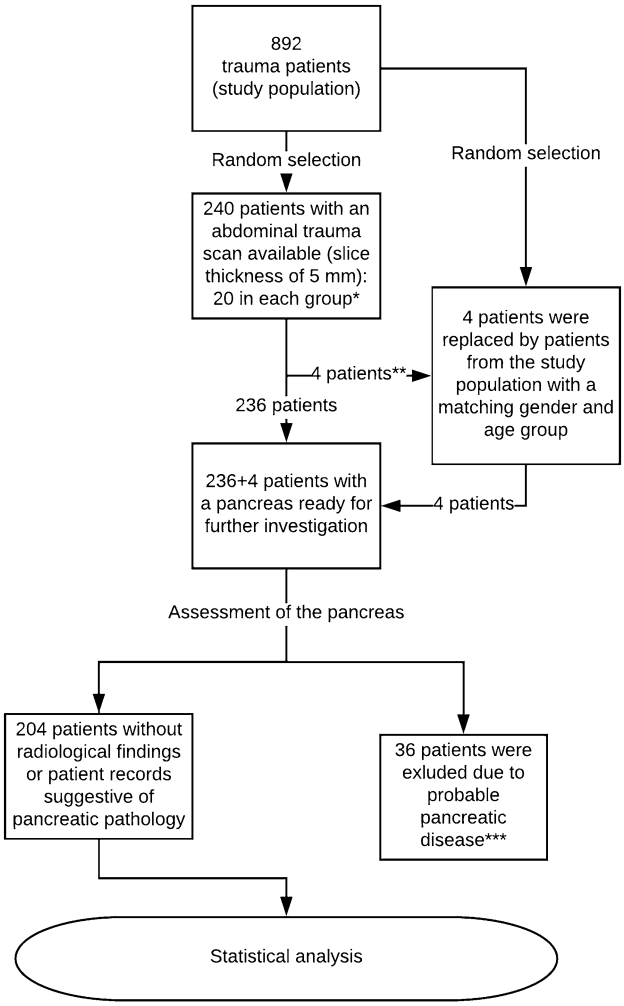

Fig. 1. Flowchart illustrating the exclusion process. Asterisk: 20 males and 20 females in every decade between 20 years of age and 80 years of age. Double asterisk: four patients were substituted because of poor visualization of their pancreas (1 with ruptured pancreas, 1 with metal screws obscuring the images and 2 with respiratory artifacts). Triple asterisk: defined as a scan presenting at least one of the following features: cystic lesions, calcifications, main pancreatic duct ≥ 5 mm or evidence of abdominal disease with a potential to affect the size or morphology of the pancreas or evidence of diabetes or prior incidence of pancreatitis found in the patients' medical records.

to investigate abdominal symptoms or any pre-existing abdominal disease.

All eligible patients had a contrast enhanced CT scan, which is part of the protocol for trauma assessment at our hospital. In case of poor image quality of the pancreas, or if the trauma involved the pancreas or its surroundings, the patient was substituted with a patient from the original pool of trauma patients of matching age and gender. Furthermore, patients with evidence of the following pancreatic pathology seen on the CT were excluded: (1) Main pancreatic duct (MPD) diame-

ter ≥ 5 mm, (2) calcifications in the pancreas, (3) cystic lesions in the pancreas, (4) atrophy/defects of the pancreatic body and tail suggestive of prior acute pancreatitis, and (5) other abdominal pathology defined as radiologically evident pathology that could affect the morphology of the pancreas (cirrhosis, enlargement of the liver, or abdominal tumors). Finally, all enrolled patients had their medical records evaluated and were excluded from the study if they had a known or suspected history of pancreatic disease, diabetes or had symptoms related to the pancreas or gastrointestinal organs.

CT image acquisition

The trauma patients were scanned using either a General Electrics scanner with 32 or 64 slices, or a Siemens scanner with 128 slices. The same protocol was used: 120 kV, automatic tube current modulation (200–750 mA), 0.5-s tube rotation, cranio-caudal direction. Every scan was performed during deep inspiration and with intravenous contrast (100 ml Iomeron® 400 mg/ml, Flowrate 4.0 ml/s). Every scan included 5 mm axial slices of chest and abdomen with manual coronal and sagittal reconstructions.

Volume assessment of the pancreas

The PV was assessed by means of the summation of areas technique using a semi-automatic approach (see Fig. 2).

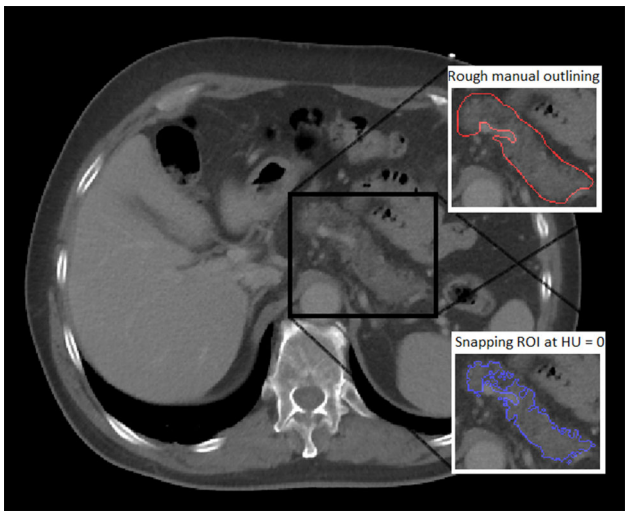

Fig. 2. Illustrating the segmentation process defining the region of interest (ROI). The red border is drawn by hand to define the area containing the pancreas without vessels. The blue border defines an area containing pancreatic tissue based on the red ROI without surrounding fat by excluding voxels around the pancreas with Hounsfield Unit (HU) values less than 0.

First, the pancreas was outlined roughly by hand on all axial slices involving the pancreas to define the location of the pancreas. Then, a customized software (a modification of the MRI pancreatic volumetry software programmed in Matlab by the MechSense research group [18]) was used to identify the outline of the pancreas. Since the pancreatic tissue has Hounsfield Unit (HU) values of > 30 and surrounding fat HU values of -50 to -150, an HU value of 0 was used as segmentation threshold. Segmentation was done on all axial slices containing pancreatic tissue, and by multiplying the area inside the regions of interest (ROI) with the 5-mm slice thickness, the total PV was determined. As the CT scans were contrast enhanced, the vessels surrounding the pancreas could easily be located and avoided when outlining the pancreas.

Two-point measurements

All two-point measurements were done in our clinical PACS system (EasyViz v. 7.4, Karos Health AS, Valby, Denmark) and included: The antero-posterior (AP) diameters of the head (Fig. 3A), body (Fig. 3B), and tail (Fig. 3C). The AP diameter of the tail was measured two centimeters from the left lateral border of the pancreas. Transverse diameter (TD) of the head (Fig. 3A) was measured on the same slice as the AP diameter at the point where the head of pancreas was largest. The TD of the body and tail combined (Fig. 3D) was measured from the tail to the anterior border of the confluence of the superior mesenteric vein and splenic vein. The cranio-caudal (CC) diameter of the head (Fig. 3E) was measured between the portal vein and the transverse duodenum. The CC diameter of the body (Fig. 3F) was measured at the largest part of the body. Both CC diameters were measured on sagittal images.

L1 vertebral measurements: a proxy of human height

Information about the height of the trauma patients was not available in this retrospective study. Therefore, the dimensions of the first lumbar vertebral body (L1) were found [19] as a proxy of the patients height [8, 20, 21]. Hence, the height, width and length of L1 (Fig. 4A) were measured.

Measurements of body composition

From an axial slice at the fourth lumbar vertebral level (L4) the cross-sectional areas (CSA) of visceral fat and subcutaneous fat were measured based on HU values (see Fig. 4B) using a semi-automatic software (VikingSlice, Aalborg University Hospital, Aalborg, Denmark) as previously described in Ozola-Zalite et al. [22]. Furthermore, the AP diameter of the ventral subcuta-

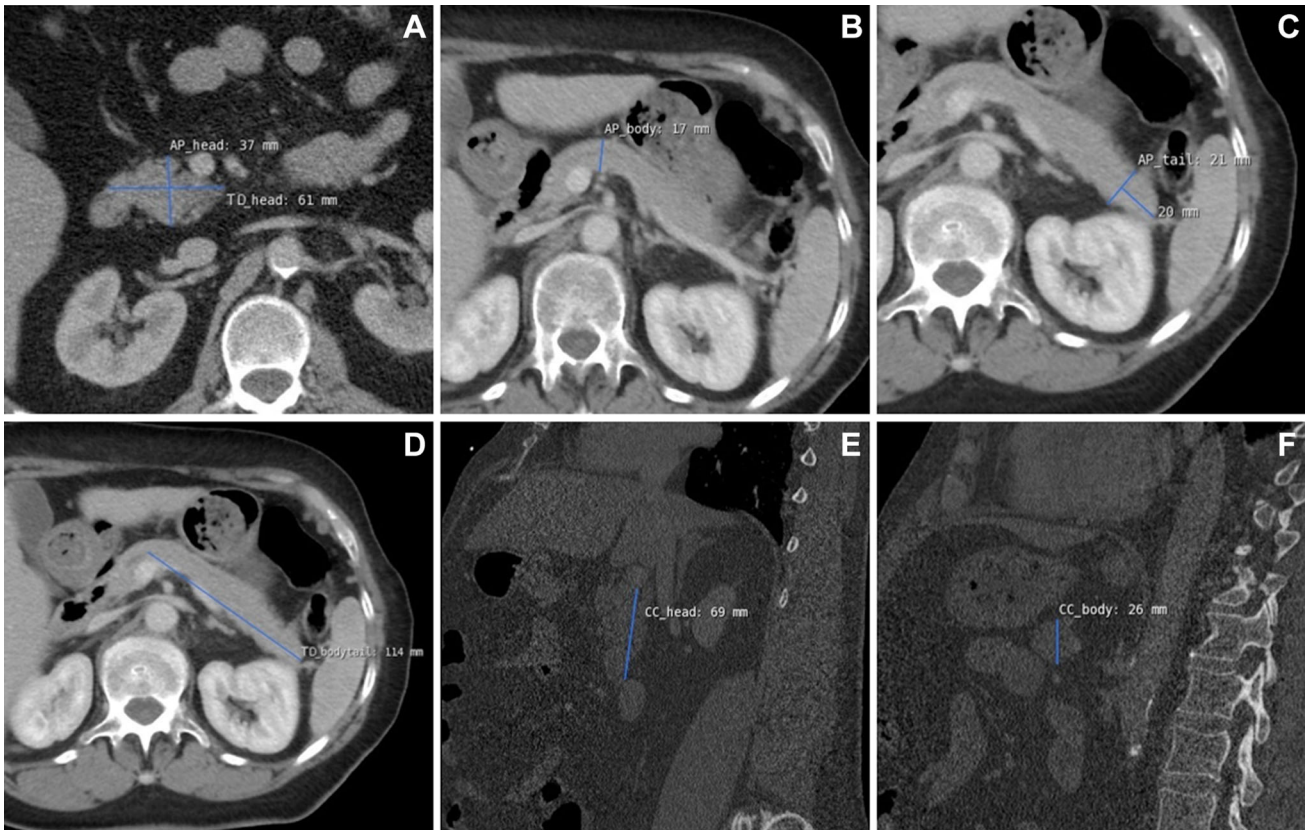

Fig. 3. Two-point measurements of the pancreas. All images depict axial slices except images **E** and **F** (sagittal reconstructions). AP, anterio-posterior; TD, transversal diameter; CC, cranio-caudal.

neous fat layer was measured in the midline at the level of L1 (not shown) as in Djuric-Stefanovic et al. [12].

Statistics

All data are presented as mean ± SD unless otherwise indicated. The assumption of normality was checked through inspection of Q–Q plots and the assumption of equal variances between groups was checked using the Bartlett's test. Analysis of variance (ANOVA) was performed to investigate the effects of age, organized by decade, and gender on PV. Associations between segmented volume and two-point measurements were analyzed using Pearson's correlation. Univariate linear regression and multivariate linear regression with stepwise backward elimination were used to analyze the associations between PV and demographic and clinical assessment parameters. The statistics were performed using STATA 15.0 (StataCorp LLC, Texas, USA).

Results

Two hundred and four patients with a normal pancreas were included for analysis (Fig. 1). Demographic data including gender distribution of all the CT measurements are shown in Table 1.

Segmented pancreatic volume by gender and age

The total mean PV was 77.9 ± 21.7 cm^3 and the minimum and maximum PVs measured in the study population were 18.8 cm^3 and 139.8 cm^3, respectively.

For women the mean volume of the pancreas was 72.3 ± 19.2 cm^3 and for men 83.7 ± 22.7 cm^3. The mean difference between the two genders (unadjusted for other variables) was 11.4 cm^3 (95% CI 5.6–17.2 cm^3; $p < 0.001$).

The pancreatic volume decreased with advancing age ($F = 3.43$; $p = 0.005$)—Fig. 5A. In addition, significant differences in PV between genders were observed ($F = 17.3$; $p < 0.001$) with smaller PV observed in women. This difference was independent of the effect attributed to age ($F = 1.71$; $p = 0.13$)—Fig. 5B.

Correlations between segmented pancreatic volume and two-point CT measurements

All two-point measurements of the pancreas correlated significantly ($p < 0.001$) with the segmented PV (see Table 2). The strongest correlation was seen for the TD of the head followed by the AP diameter of the head (correlation coefficients 0.50 and 0.47, respectively, both

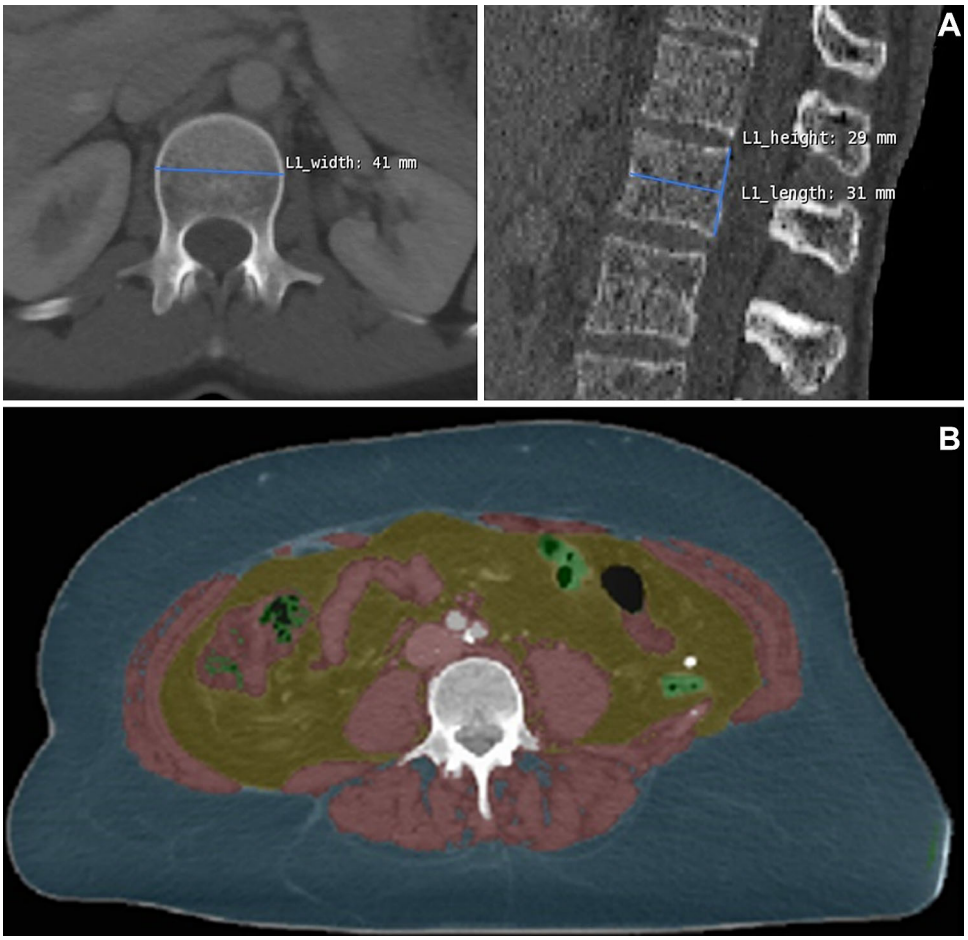

Fig. 4. Indicators of anthropometric profiles. **A** Measurements of the L1 vertebral body (height, width and length). **B** Body composition—axial slice at the level of L4. Yellow: intraabdominal/visceral fat. Blue: extra abdominal fat (primarily subcutaneous fat outside the peritoneum/retroperitoneum). Green: intra-intestinal content (the intestines with fecal material of same HU value as fat). Red and white: Other tissues (e.g., muscles, intestines, and bones).

Table 1. Demographics and body composition of the study population

	Total	Male	Female
Number	204	100	104
Age (years)	48.3 ± 17.2	49.1 ± 17.4	47.5 ± 16.9
Pancreatic volume (cm^3)	77.9 ± 21.7	83.7 ± 22.7	72.3 ± 19.2
CSA visceral fat (cm^2)	113.3 ± 91.6	133.4 ± 100.1	93.9 ± 78.5
CSA subcutaneous fat (cm^2)	255.6 ± 132.1	218.2 ± 115.0	291.5 ± 138.0
Thickness of abdominal subcutaneous fat (mm)	20.4 ± 10.5	16.1 ± 9.0	24.5 ± 10.2
Width of L1 body (mm)	39.3 ± 4.0	42.1 ± 3.0	36.6 ± 2.8
Height of L1 body (mm)	28.9 ± 2.1	29.8 ± 2.0	28.0 ± 1.8
Length of L1 body (mm)	30.3 ± 3.5	32.4 ± 3.1	28.3 ± 2.6

Values are mean ± SD
CSA, cross-sectional area; L1, 1st lumbar vertebra

$p < 0.001$). The TD of the pancreatic head ranged from 16 to 59 mm.

Uni- and multivariate analysis of factors potentially affecting pancreatic volume

On the univariate analysis, gender ($p < 0.001$), all three L1 vertebral body dimensions ($p < 0.001$), visceral fat cross-sectional area ($p = 0.004$), and age ($p = 0.043$) were associated with PV—Table 3. Multivariate analysis confirmed the independence and significance of the associations for age, L1-width and visceral fat cross-sectional area (all $p < 0.001$)—Table 3. Thus, the following parameters were eliminated in the multivariate model: gender ($p = 0.441$), subcutaneous fat cross-sectional area ($p = 0.387$), L1-length ($p = 0.373$), L1-

height ($p = 0.107$) and the AP diameter of the ventral subcutaneous fat layer ($p = 0.080$).

Discussion

Both the pancreatic volume and the various two-point measurements of the pancreas showed a large interindividual variation. In general, the PV was smaller in women; however, this difference became insignificant when adjusting for anthropometric parameters. Thus, the PV was independently associated with age, the width of the L1 vertebral body and visceral fat content, while gender had no independent influence on PV.

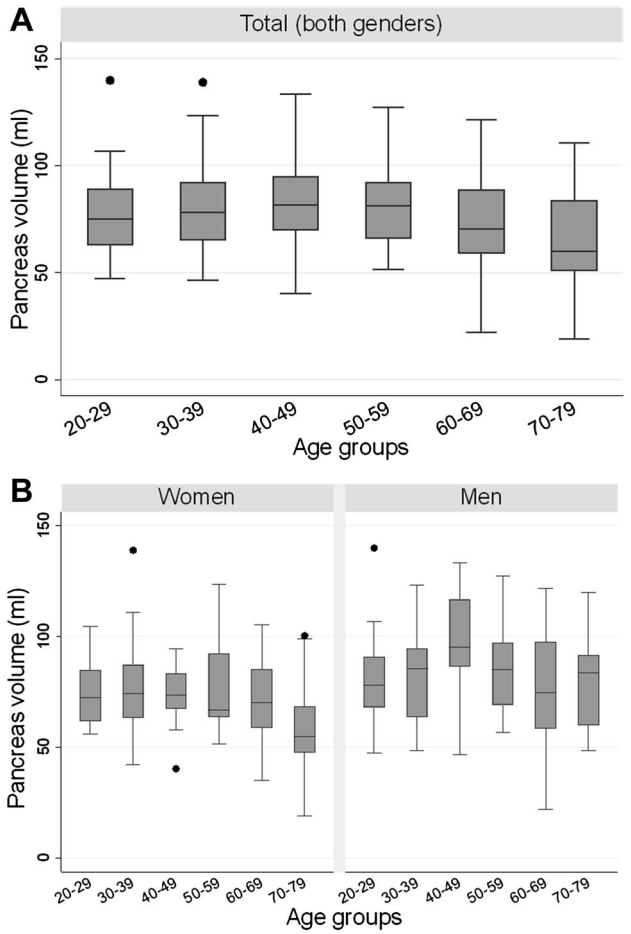

Fig. 5. Dividing the patients into decades of age from 20 to 80 years of age, the volume of the pancreas is visualized in a boxplot showing the 25th percentile, median, 75th percentile and upper- and lower adjacent values. This is shown for both genders combined (**A**) and separately (**B**).

Pancreatic volume and variability

The mean PVs found in our study are comparable to the results of previous studies. In a study by Djuric-Stefanovic et al. the mean segmented PV was 79.2 ± 24.1 cm^3 ($n = 220$ adults), which is highly comparable to our findings [12]. Similar findings were found in a study among 660 healthy controls (non-diabetics) with a mean volume of 74.9 ± 27.0 cm^3 (54% females which might explain the lower mean volume) [14]. In another study based on 272 patients without pancreatic pathology, mean volumes were 71.8 ± 16.0 cm^3 in men and 63.7 ± 15.1 cm^3 in women [11]. The lower mean volumes in their study may be explained by the inclusion of 32 people older than 80 years of age having a mean volume of 52.5 cm^3.

While the mean PVs seem relativity similar across studies, it is important to notice that the mean values comprise a large interindividual variability in PV, which precludes the establishment of narrow and clinically useful reference intervals.

Factors associated with pancreatic volume

Significant and independent associations to PV were observed for age, L1-width (a proxy for human height) and visceral fat, while no independent association was observed between PV and gender using a multivariate model.

The changes in PV from decade to decade in the present study are insignificant. However, PV decreases significantly with age from 20 to 80 years of age, with the most abundant decrement appearing in the last two decades—Fig. 5A. This is in agreement with previous studies, finding the negative influence of age on PV to be most significant after 60 years of age, whereas the volume was largely constant from the age of 20–60 years [11, 14].

Table 2. Pearson's correlation between segmented volumes of the pancreas and 7 two-point CT measurements

Part of the pancreas	Mean ± SD	Min	Max	Correlation coefficient*
TD head (mm)	41.8 ± 6.6	16	59	0.500
AP head (mm)	25.8 ± 5.2	15	40	0.470
AP body (mm)	19.7 ± 4.0	9	30	0.422
AP tail (mm)	20.4 ± 4.5	10	34	0.433
TD bodytail (mm)	112.6 ± 16.2	74	151	0.326
CC head (mm)	51.1 ± 8.2	28	72	0.343
CC body (mm)	30.4 ± 5.4	19	48	0.283

TD, transverse diameter; AP, anterior–posterior diameter; CC, cranio-caudal diameter
*All correlation coefficients have a p value < 0.001

Table 3. Uni- and multivariate analysis of variables with a possible effect on pancreatic volume (cm^3)

Variables introduced	Coefficient (95% confidence interval)	*p* value
Univariate analysis		
Age (years)	− 0.180 (− 0.354 to − 0.027)	0.043
Male gender (cm^3)[a]	11.369 (5.565 to 17.173)	< 0.001
L1 width (mm)[b]	1.893 (1.192 to 2.594)	< 0.001
L1 height (mm)[b]	2.807 (1.397 to 4.216)	< 0.001
L1 length (mm)[b]	1.832 (1.006 to 2.657)	< 0.001
Subcutaneous fat (cm^2)[c]	0.016 (− 0.007 to 0.038)	0.175
Visceral fat (cm^2)[d]	0.047 (0.015 to 0.080]	0.004
Subcutaneous fat AP (mm)	− 0.119 (− 0.407 to 0.168)	0.415
Multivariate analysis[e]		
Age	− 0.410 (− 0.581 to − 0.238)	< 0.001
L1 width	1.987 (1.304 to 2.671)	< 0.001
Visceral fat	0.061 (0.028 to 0.093)	< 0.001

[a]Male gender volume is calculated as difference between mean volume in males and females
[b]L1 width, L1 height and L1 length are dimensions of the corpus of the first lumbal vertebrae
[c]Subcutaneous fat area and Visceral fat area constitutes areas of the abdomen at the L4-level
[d]Subcutaneous fat AP is the antero-posterior thickness of the ventral subcutaneous fat at L1-level
[e]Based on all variables introduced in the univariate regression model with a P value of < 0.05 after stepwise elimination of insignificant variables e.g., gender ($p = 0.441$), $R^2 = 0.226$ for the multivariate analysis

Pancreatic volume has previously been shown to correlate positively with BMI [11]. Similarly, our findings demonstrate a positive correlation between PV and visceral fat CSA at L4-level. Measuring visceral fat at this level predicts total visceral fat [23] and thus it is a reasonable indicator of body composition. The present study demonstrates that visceral fat is superior to subcutaneous fat in predicting PV. Measuring visceral fat could be more reliable for evaluating pancreatic size in a clinical setting than using weight or BMI, since these parameters do not differentiate between muscle mass, visceral, or subcutaneous fat. However, further research is needed to confirm this.

Furthermore, the width of L1 positively correlated with PV in the multivariate regression model. This finding is in agreement with findings in a previous study by Nakamura et al. investigating PV and human height [17]. L1 width did outperform L1 height and L1 length in the multivariate analysis; this may reflect that L1 width is a better proxy of the size of the central body and the visceral organ sizes than L1 height. Additionally, L1 width is known to be stable during aging, while L1 height is known to decrease during aging, which could affect the regression [24].

Interestingly, when controlling for age and indicators of body composition in the present study, gender did not have an independent, significant influence on PV. This has also been suggested previously in a Japanese study [17], where ratios between PV and body height were identical between men and women. Hence, the findings of a smaller pancreas in women, could simply be explained by the fact that women have a smaller body size and less visceral fat. Taken together, future studies using PV as an assessment parameter, should consider a unisex model by including simple variables such as age, height, and body composition. Additionally, the effect of weight and/or waist circumference should be explored as these parameters are available in the clinical setting and less time-consuming to record than segmentation of body composition.

Even though the pancreatic two-point measurements are moderately correlated to PV, the agreement is not absolute. These simple measurements, however, might still be useful when pancreatic size is evaluated in a clinical setting with limited time available. By tradition, the AP diameters of head and body are typically used as quick indicators of pancreatic size. In our study, the mean value of AP head diameter was 25.8 ± 5.2 mm and AP body diameter 19.7 ± 4.0 mm, which is comparable to the findings in Djuric-Stefanovic et al. [12] with 28.0 ± 5.5 mm and 21.4 ± 5.0 mm, respectively. However, the minimum and maximum diameters measured in our population were 15–40 mm for AP head and 9–30 mm for AP body, which highlights the great challenge in determining what is normal.

Some of the variation in pancreatic size within the general population is likely explained by the differences in height, weight and age, as indicated in our results. Considering the present study, it is not advised to assess the normality of pancreatic size based solely on the PV or two-point measurements. Adjusting for age, height and weight when determining the normal size of pancreas in future studies, may lead to less variation and help detect pathological changes.

From a clinical point of view, it should be considered how adjustment for body size and body composition could be integrated in the daily routine. Firstly, detailed assessment of pancreatic size is only relevant in a minority of abdominal CT studies (for instance in the suspicion of CP). Secondly, data on height, weight, and

BMI are easily available compared to more time-consuming measurements of visceral fat and vertebral dimensions. However, this can be optimized and potentially integrated in the image reading software. For instance, a given pancreatic volume (or AP diameter) could be normal in a small person with little visceral fat, while the same volume could be too small (indicating atrophy and maybe mild CP) in a large person with much visceral fat at same age. Indeed, future studies are needed to address the clinically usefulness of different strategies (simple vs. more complex) when adjusting pancreatic size for body size and body composition.

Limitations

The reproducibility of our pancreatic measurements has not been tested with other observers, but the segmentation method resembles the one used in the study by Lim et al. [2] where a high inter-reader agreement was reported (correlation coefficient $r = 0.96$ in 50 subjects).

The use of trauma patients to represent a random sample of the general population provides the opportunity to analyze CT scans of people without pre-existing symptoms or disease. However, excessive alcohol consumption is a risk factor of being a trauma patient [25] and alcoholic patients may have a larger pancreas due to acute inflammation, or it may be reduced because of early stages of chronic pancreatitis. If such patients are overrepresented, it could bias our study. However, this issue is partly prevented by the exclusion of patients with radiological signs of abdominal or pancreatic pathology and exclusion of patients with diabetes or previous incidences of pancreatitis by reviewing the patient records.

Unfortunately, human height and weight were not available. Instead, the visceral and subcutaneous fat cross-sectional areas were measured. Previous studies have shown good correlation between cross-sectional fat areas in a single abdominal slice and total abdominal fat [26, 27], and the method is well-established in nutritional research. Hence, most nutritionists recommend the use of body composition techniques for assessment of nutritional state rather than BMI [28]. As a surrogate for height, the dimensions of L1 were measured, which have shown strong correlations to human height and have been used in several studies [8, 20, 21]. The advantage of this approach is, however, that all necessary information about the body is found within the CT scan.

Regarding external validity, it is reasonable to consider the mean PV in the present study to be valid for the healthy general population in western countries and other countries with similar demography. The associations between PV and age and body composition will likely apply to most populations in the world but needs further evaluation in other subgroups.

Conclusions

The present study utilized a semi-automatic method to assess the pancreatic volume based on a routine CT scan. The pancreatic volume was associated with age, human height and visceral fat content, while gender had no independent influence on the pancreatic volume. The interindividual variation of PV was large. This indicates that establishment of narrow and clinically useful reference intervals for PV will be difficult. A standardized analysis approach of human pancreatic volume may in the future prove to be useful in the diagnosis and monitoring of pancreatic diseases. Therefore, the pancreatic size should be evaluated in the context of anthropometric profiles.

Compliance with ethical standards

Disclosure The authors declare no conflict of interest.

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