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HEPATOBILIARY-PANCREAS

# Psoas muscle size as a magnetic resonance imaging biomarker of progression of pancreatitis

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## Abstract

**Objective** Pancreatitis often represents a continuous inflammatory process, from the first episode of acute pancreatitis (FAP) to recurrent acute pancreatitis (RAP) to chronic pancreatitis (CP). Psoas muscle size is a validated surrogate for global skeletal mass, changes in which are associated with inflammation. The objective was to investigate psoas muscle size in individuals following FAP, RAP, and CP, as well as its associations with pro-inflammatory cytokines.

**Methods** Individuals following pancreatitis and healthy individuals were recruited. All participants underwent magnetic resonance imaging, from which psoas muscle volume was derived independently by two raters in a blinded fashion. Circulating levels of four major cytokines (interleukin-6, tumour necrosis factor-α, C-C motif chemokine ligand 2, and leptin) were measured. Five linear regression additive models were built to adjust for possible confounders (age, sex, body composition, physical activity, tobacco smoking, alcohol consumption, comorbidities, and endocrine and exocrine pancreatic functions).

**Results** A total of 145 participants were enrolled. A significant downward trend in psoas muscle volume was observed between healthy controls and individuals following FAP, RAP, and CP in all adjusted models ($p = 0.047$, 0.005, 0.004, and $< 0.001$). Leptin was significantly associated with psoas muscle volume in all models ($\beta = -0.16$, $p = 0.030$ in the most adjusted model). The other studied cytokines were not significantly associated with psoas muscle volume.

**Conclusions** Psoas muscle size is significantly reduced along the continuum from FAP to RAP to CP. Leptin appears to be one of the factors implicated in this. Further studies are warranted to investigate the relationship between skeletal muscle and inflammation of the pancreas.

**Key Points**

- *First acute pancreatitis, recurrent acute pancreatitis, and chronic pancreatitis were associated with progressively reduced psoas muscle size.*
- *The findings were independent of age, sex, body fat composition, physical activity, tobacco smoking, alcohol consumption, comorbidities, and exocrine and endocrine functions of the pancreas.*
- *The mechanism underlying the observed findings may involve hyperleptinaemia.*

**Keywords** Magnetic resonance imaging · Pancreas · Pancreatitis · Biomarkers · Psoas muscle

**Abbreviations**

| | |
|---|---|
| ACCI | Age-adjusted Charlson comorbidity index |
| BMI | Body mass index |
| CCL2 | C-C motif chemokine ligand 2 |
| CI | Confidence interval |
| CP | Chronic pancreatitis |
| FAP | First episode of acute pancreatitis |
| HbA1c | Glycated haemoglobin |
| ICC | Intraclass correlation coefficient |
| IL-6 | Interleukin 6 |
| IQR | Interquartile range |

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| | |
|---|---|
| PMI | Psoas muscle index |
| PMV | Psoas muscle volume |
| RAP | Recurrent acute pancreatitis |
| TNFα | Tumour necrosis factor-α |
| SFV | Subcutaneous fat volume |
| VFV | Visceral fat volume |
| V/S | Visceral to subcutaneous (fat volume ratio) |

## Introduction

Pancreatitis is a frequent inflammatory disease, with the annual global incidence of acute pancreatitis being 34 cases and chronic pancreatitis (CP)—10 cases per 100,000 people in the general population [1]. The incidence of pancreatitis is generally a function of age, with the 65+ years age group most affected [2, 3]. Pancreatitis often lies on a continuum, with 22% of individuals with the first episode of pancreatitis (FAP) subsequently developing recurrent episodes of acute pancreatitis (RAP) and 36% of individuals with RAP subsequently developing CP [4]. Chronic pancreatitis, a disease characterised by irreversible morphologic changes in its advanced stage, often leads to new-onset diabetes after pancreatitis and pancreatic cancer (especially in elderly people) [5]. While there are limited therapeutic options in the advanced stage of CP, patients with early CP are positioned well to benefit from interventions that have the potential to prevent the progression to advanced CP and its sequelae [6]. Given the chronicity of pancreatitis and taking into account that it is a strong risk factor for pancreatic cancer and a common cause of new-onset diabetes, there is a pressing clinical need to have a relatively quick, widely available, non-invasive, and quantitative early biomarker of chronic pancreatitis. Such a biomarker would be a cornerstone of the 'holistic prevention pancreatitis' framework [7].

Sarcopenia, a syndrome characterised by reduced skeletal muscle size and/or strength, was initially studied in relation to ageing only. More recent research have also found that it is an independent predictor of poor clinical outcomes in a range of diseases, such as heart disease [8], end-stage liver disease [9], metastatic colorectal cancer [10], and chronic kidney disease [11]. Moreover, sarcopenia is linked to a reduced survival rate in malignant diseases, including pancreatic cancer [12–15], and is a predictor of postoperative complications following pancreatic resection or pancreas transplantation [16–19]. In pancreatitis setting, sarcopenia is significantly associated with severity of acute pancreatitis, increased in-hospital mortality in acute necrotising pancreatitis, and reduced survival in CP patients [20, 21]. The factors leading to reduced skeletal muscle size in pancreatitis are not completely understood yet; however, some studies showed that it is inversely associated with pro-inflammatory cytokines [22, 23]. Notably, to date, all the studies on sarcopenia in pancreatitis setting have focused on either acute or chronic disease, not a continuum from FAP to CP through RAP.

The gold standard for studying skeletal muscle size in the context of sarcopenia is dual-energy X-ray absorptiometry-derived appendicular lean mass [24]. However, this method is not routinely available in non-academic settings and exposes participants to radiation risk. Abbreviated methods to screen for reduced skeletal muscle size have been proposed [25–27]. Psoas muscle, a core muscle that correlates well with handgrip strength and gait speed, has emerged as a novel validated surrogate for global skeletal mass [28, 29]. It can be easily measured with the use of magnetic resonance (MR) imaging that is already an essential part of the diagnostic armamentarium for CP. However, MR imaging is currently used mainly to identify conventional features of CP (such as dilated main pancreatic duct, abnormal side branches, cavitation) and the possibility to use it opportunistically to measure skeletal muscle size has been overlooked. To the best of our knowledge, no study has investigated the clinical usefulness of using MR imaging to measure psoas muscle size in the setting of pancreatitis.

The primary aim was to compare MR-derived psoas muscle size between individuals following FAP, RAP, and CP and healthy controls (taking into account age, body composition, and other relevant covariates). The secondary aim was to investigate the associations between psoas muscle size and circulating levels of major pro-inflammatory cytokines.

## Methods

### Study design

This was a cross-sectional study as part of the ARIES project. Eighteen years old or older patients who had been diagnosed with pancreatitis were eligible for the study. The diagnosis of acute pancreatitis was established based on the presence of two of the following three criteria: serum lipase and/or amylase at least three times the upper limit of normal; pain suggestive of acute pancreatitis; and characteristic imaging findings of acute pancreatitis. The diagnosis of CP was established based on the presence of ductal or parenchymal calcifications on modern imaging and/or Cambridge grade ≥ 3. The exclusion criteria are detailed in the Supplement. Individuals following pancreatitis were categorised into the FAP, RAP, and CP groups. The FAP group included individuals with a single episode of acute pancreatitis by the time of the study; the RAP group included individuals with two or more episodes of acute pancreatitis by the time of the study; and the CP group included individuals who met the above criteria for definite CP. Readmission for acute pancreatitis within 30 days after the previous hospital discharge for acute pancreatitis was not counted as a new episode. Individuals with acute pancreatitis

and CP were mutually exclusive, and the priority was given to CP when a patient met the criteria for both diagnoses. This means that a patient that progressed from acute pancreatitis to CP was deemed to have CP only for the purpose of the present study. Healthy participants were also recruited as the control group. Their eligibility criteria are detailed in the Supplement.

## MR-derived variables

All participants underwent abdominal MR scans using 3.0-T MAGNETOM Skyra® scanner (Siemens). The image acquisition protocol was described in detail elsewhere [30–33]. Psoas muscle volume (PMV) was calculated in $cm^3$ by measuring the right and left psoas major muscle area bilaterally from the second lumbar vertebral level to the fifth lumbar vertebral level and multiplying by the thickness of MR slices (3 mm) [27]. Exemplar psoas muscle measurements are presented in Fig. 1. Given that psoas muscle size was associated with participants' anthropometrics in previous studies [27, 34], the psoas muscle index (PMI) was used in addition to PMV as a dependent variable. The PMI was calculated by dividing the total PMV by the individual's height squared. Height was not statistically associated with the groupings ($p = 0.653$) and did not act as a confounder in the present study. Visceral to subcutaneous (V/S) fat volume ratio was also calculated using subcutaneous fat volume (SFV) and visceral fat volume (VFV), as described in detail elsewhere [30].

Two raters, blinded to participant characteristics and group allocation, measured PMV, SFV, and VFV independently. Average measurement values of the two measurements were used for all statistical analyses. Intra-class correlation coefficient (ICC) was used to evaluate the inter-rater reliability of measurements. Intra-class correlation coefficient of < 0.5, 0.5–0.75, 0.75–0.9, and > 0.9 was indicative of poor, moderate, good, and excellent inter-rater reliability, respectively [35, 36].

## Other variables

Circulating levels of interleukin-6 (IL-6), chemokine ligand 2 (CCL2), tumour necrosis factor-α (TNFα), and leptin were measured at the time of the study. In addition, blood samples were analysed for glycated haemoglobin (HbA1c) and pancreatic amylase. Details on laboratory measurements and the definitions of other study variables are presented in the Supplement.

## Statistical analyses

All analyses were performed using SPSS for Windows Version 25 (SPSS Inc.). The extreme values (as assessed by cases with values/standardised residuals greater than ± 3

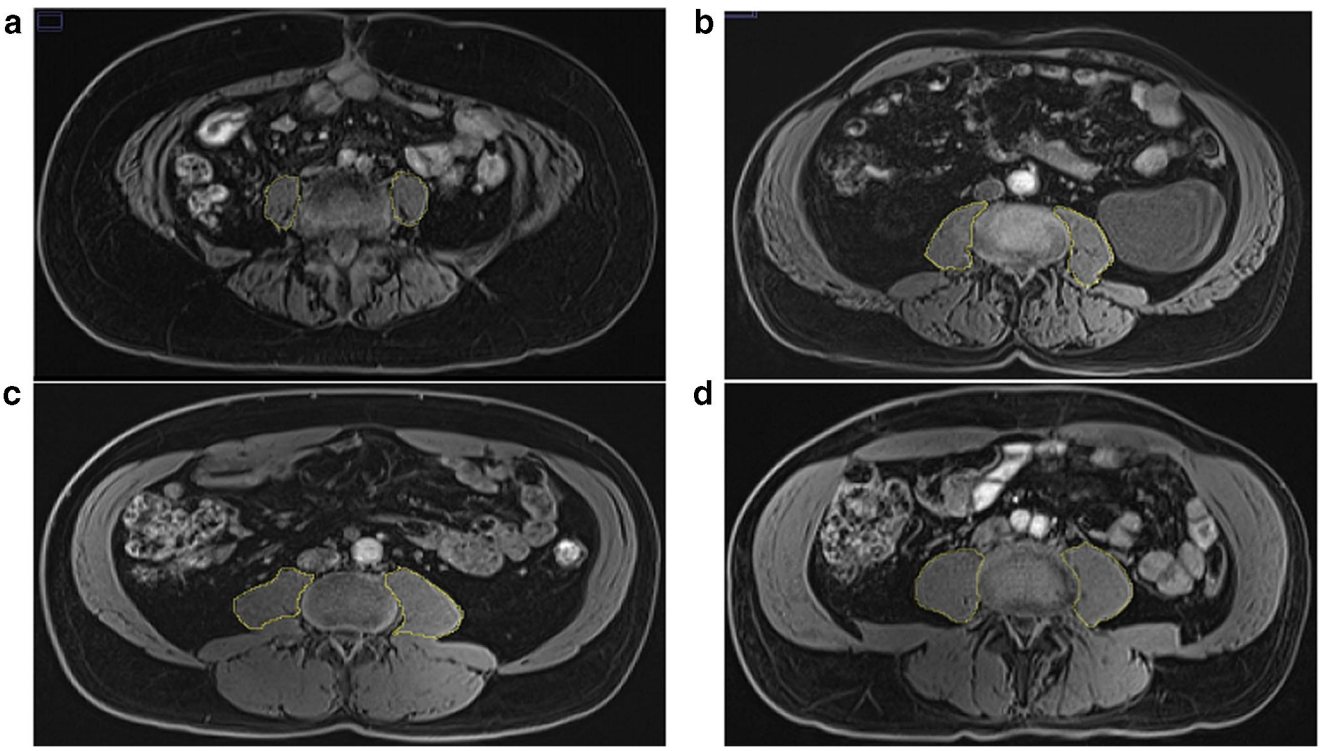


**Fig. 1** Psoas muscle measurements (cranial aspect of the L3-L4 intervertebral disk) in the study groups. **a** Individual with chronic pancreatitis (PMV = 84 $cm^3$; PMI = 33 $cm^3/m^2$). **b** Individual with recurrent acute pancreatitis (PMV = 226 $cm^3$; PMI = 93 $cm^3/m^2$). **c** Individual with first episode of acute pancreatitis (PMV = 296 $cm^3$; PMI = 109 $cm^3/m^2$). **d** Healthy control individual (PMV = 396 $cm^3$; PMI = 111 $cm^3/m^2$). *PMV*, psoas muscle volume; *PMI*, psoas muscle index

standard deviations) were regarded as outliers and were excluded from the analyses [37]. Individuals who had PMV < 5 percentiles (83.5 $cm^3$) or > 95 percentiles (398.5 $cm^3$) were excluded from the analyses. The differences in baseline characteristics between the study groups were examined using analysis of variance (continuous variables) and chi-squared test (categorical variables).

To investigate the differences in PMV and PMI between each of the pancreatitis group (FAP, RAP, and CP) and the healthy control group (i.e. primary aim), five linear regression models were constructed, with healthy controls as the reference group. Model 1 was unadjusted; model 2 was adjusted for age and sex. Model 3 was adjusted for the model 2 variables as well as V/S fat ratio and HbA1c. Model 4 was adjusted for the model 3 variables as well as physical activity status, serum pancreatic amylase, and age-adjusted Charlson comorbidity index (ACCI). Model 5 was adjusted for the model 4 variables as well as smoking status and alcohol consumption. To determine the trend across the study groups, a linear regression was applied to each model treating a categorical variable that classified participants according to their study group (in the following order—healthy controls, FAP, RAP, and CP) as the dependent variable.

To investigate the associations of PMV and PMI with pro-inflammatory cytokines in individuals with pancreatitis (i.e. secondary aim), linear regression analysis was conducted. In this analysis, the models described above were built. Data from the linear regression models were presented as beta coefficients (i.e. median difference in PMV or PMI between each of the pancreatitis group and healthy controls group), standard errors, $R^2$ metrics of the overall model, and $p$ values. Statistical significance was set as two-sided $p < 0.05$ in all analyses.

## Results

### Characteristics of participants

A total of 106 individuals following AP or CP were included in the study, comprising 71 men and 35 women. The median (interquartile range, IQR) age was 57 (45–69) years, the median (IQR) BMI was 27.5 (23–31) $kg/m^2$, and the median (IQR) HbA1c was 38 (35–41) mmol/mol. Of the 106 individuals, 73 had FAP, 23 had RAP, and 10 had CP. Thirty-nine healthy controls, comprising 20 men and 19 women, were also included. Their median (IQR) age was 47 (33–60) years, the median (IQR) BMI was 24.1 (20.6–27.6), and the median (IQR) HbA1c was 33 (30.5–35.5) mmol/mol. Other characteristics are presented in Table 1.

### Inter-rater reliability

The ICC (95% confidence interval, CI) for PMV was 0.982 (0.974–0.988), for VFV 0.996 (0.994–0.997), and for SFV 0.997 (0.996–0.998) (Fig. 2).

### Psoas muscle volume

Mean PMV was 238 ± 51 $cm^3$ in the CP group, 258 ± 25 $cm^3$ in the RAP group, 251 ± 16 $cm^3$ in the FAP group, and 261 ± 27 $cm^3$ in the healthy control group. The difference in PMV was not statistically significant in the unadjusted model ($p$ trend = 0.480). However, it was statistically significant in all the adjusted models ($p$ trend = 0.047, 0.005, 0.004, and < 0.001 in models 2, 3, 4, and 5, respectively). The differences in PMV between each pancreatitis group individually and healthy control group are presented in Table 2.

### Psoas muscle index

The mean PMI was 78.3 ± 16.1 $cm^3/m^2$ in the CP group, 88.6 ± 7.9 $cm^3/m^2$ in the RAP group, 84.4 ± 4.6 $cm^3/m^2$ in the FAP group, and 91.3 ± 7.7 $cm^3/m^2$ in the healthy control group. The difference in PMI was not statistically significant in the unadjusted model ($p$ trend = 0.151). However, it was statistically significant in all the adjusted models ($p$ trend = 0.004, 0.018, 0.019, and 0.004 in models 2, 3, 4, and 5, respectively). The differences in PMI between each pancreatitis group individually and healthy control group are presented in Table 2.

### Associations between psoas muscle size and pro-inflammatory cytokines

Leptin was significantly associated with both PMV and PMI in the unadjusted models ($p = 0.016$ and $p = 0.020$, respectively). Also, it was significantly associated with PMV in all the adjusted models, and with PMI in models 2 and 5 (Table 3). Interleukin-6 was significantly associated with PMV in model 3 only, but not in the unadjusted or the other adjusted models. It was not significantly associated with PMI in any of the models (Table 3). TNFα and CCL2 were not significantly associated with either PMV or PMI in any of the studied models.

## Discussion

The present study investigated the relationship between psoas muscle size and progression of pancreatitis. Both PMV and PMI (derived from MR imaging) demonstrated significant downward trends from healthy controls to FAP, RAP, and CP individuals, when adjusted for age, sex, body fat distribution, physical activity, tobacco smoking, alcohol

**Table 1** Characteristics of the study groups

| Characteristic | FAP ($n = 73$) | RAP ($n = 23$) | CP ($n = 10$) | Healthy controls ($n = 39$) | $p$ |
|---|---|---|---|---|---|
| Age (years) | 55 (43–67) | 60 (48–72) | 54 (48–62) | 47 (33–61) | 0.103 |
| Sex | | | | | 0.195 |
| Men | 46 (61.1%) | 17 (73.9%) | 8 (80.0%) | 20 (51.28%) | |
| Women | 27 (38.9%) | 6 (26.1%) | 2 (20.0%) | 19 (48.72%) | |
| BMI (kg/m$^2$) | 27.5 (23.0–31.0) | 27.6 (23.6–31.6) | 25.1 (21.6–28.6) | 24.1 (20.6–27.6) | *0.022* |
| HbA1c (mmol/mol) | 38.0 (35.0–41.0) | 38.5 (33.5–43.5) | 38.5 (31.5–45.5) | 33 (30.5–35.5) | *< 0.001* |
| V/S fat volume ratio | 0.69 | 0.75 | 1.09 | 0.36 | *< 0.001* |
| Physical activity | | | | | 0.809 |
| Inactive | 31 (49.2%) | 10 (55.6%) | 5 (55.6%) | 14 (45.2%) | |
| Active | 32 (50.8%) | 8 (44.4%) | 4 (44.4%) | 17 (54.8%) | |
| Smoking status | | | | | *0.007* |
| Never | 32 (43.8%) | 8 (34.8%) | 3 (30.0%) | 23 (59.0%) | |
| Former | 29 (39.7%) | 6 (28.1%) | 4 (40.0%) | 11 (28.2%) | |
| Light | 5 (6.8%) | 2 (9.1%) | 3 (30.0%) | 5 (12.8%) | |
| Moderate | 3 (4.2%) | 6 (28.1%) | 0 (0%) | 0 (0%) | |
| Heavy | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | |
| ACCI | 1(0–3) | 2 (0.5–3.5) | 1.5 (0.5–2.5) | 0 (0–1) | *0.008* |
| Alcohol consumption (U/week) | 12 (0–140) | 72 (0–246) | 336 (96–596) | 2 (0–12) | *0.002* |
| Aetiology | | | | | *< 0.001* |
| Biliary | 39 (53.4%) | 6 (26.1%) | 1 (10.0%) | N/A | |
| Non-biliary | 34 (46.6%) | 17 (73.9%) | 9 (90.0%) | N/A | |
| Pancreatic amylase (U/l) | 14.1 (6.6–21.6) | 20.0 (12.5–27.5) | 14.9 (8.9–22.9) | 20.6 (12.1–29.1) | 0.350 |
| IL-6 (pg/ml) | 10.0 (5.0–10.0) | 5.5 (1.0–10.0) | 8.5 (6.5–10.5) | 11.7 (5.2–18.2) | 0.259 |
| TNF$\alpha$ (pg/ml) | 5.3 (3.3–7.3) | 6.1 (3.6–8.6) | 6.4 (4.4–8.4) | 5.2 (3.7–6.7) | 0.759 |
| Leptin (ng/ml) | 6.2 (0.7–11.7) | 3.8 (1.8–5.8) | 20.0 (0–2065.0) | 2.9 (0–6.4) | *< 0.001* |
| CCL2 (pg/ml) | 100.2 (57.7–143.7) | 108.5 (73.0–144) | 57.1 (24.6–89.5) | 68.2 (38.7–97.7) | 0.421 |

Data are presented as median and interquartile range or frequency count and percentages. *P* values were from analysis of variance (continuous variables) and chi-squared test (categorical variables). Statistically significant ($p < 0.05$) differences are shown in italics

*FAP*, first episode of acute pancreatitis; *RAP*, recurrent acute pancreatitis; *CP*, chronic pancreatitis; *BMI*, body mass index; *HbA1c*, glycated haemoglobin; *V/S*, visceral to subcutaneous fat volume ratio; *ACCI*, age-adjusted Charlson index; *N/A*, not applicable; *IL-6*, interleukin 6; *TNF$\alpha$*, tumour necrosis factor-$\alpha$; *CCL2*, C-C motif chemokine ligand 2

consumption, markers of glucose metabolism and exocrine pancreatic function, and the ACCI. Further, we investigated the possible involvement of four major cytokines and found that serum leptin is significantly associated with psoas muscle size, in both the unadjusted and adjusted analyses. These results have implications for both practice and research.

The progressive reduction of PMV (and PMI) was a novel finding. Specifically, we found that, when compared with healthy control, FAP individuals have PMV reduced by 42 cm$^3$, RAP individuals have PMV reduced by 55 cm$^3$, and CP individuals have PMV reduced by 94 cm$^3$ (in the most adjusted model that takes into account all the covariates mentioned above). One practical implication of this finding is that PMV has the potential to be used as a quick quantitative MR biomarker of pancreatitis progression. Identification of a progressive PMV reduction during follow-up of the same individual could be a harbinger of early CP. This is important because, while MR imaging, computed tomography, endoscopic ultrasound, and ERCP have similar sensitivity in the setting of CP [38], the last two are more invasive and expensive than the first two alternatives. Computed tomography carries the disadvantage of additional radiation (during repeated follow-ups). Hence, measuring PMV on abdominal MR imaging could increase its diagnostic yield in individuals with progression of pancreatitis (without a need for any change in MR scan protocol or duration of the scan). Importantly, PMV measurements are highly reproducible, as evidenced by the ICC of 0.98 in the present study. Purposely designed longitudinal studies are now warranted to investigate the diagnostic accuracy of MR-derived PMV in CP before its use can be recommended for routine clinical practice.

While the pathogenesis of reduced psoas muscle size following pancreatitis also needs to be investigated in future studies, one pathway likely involves hypersecretion of leptin. This is

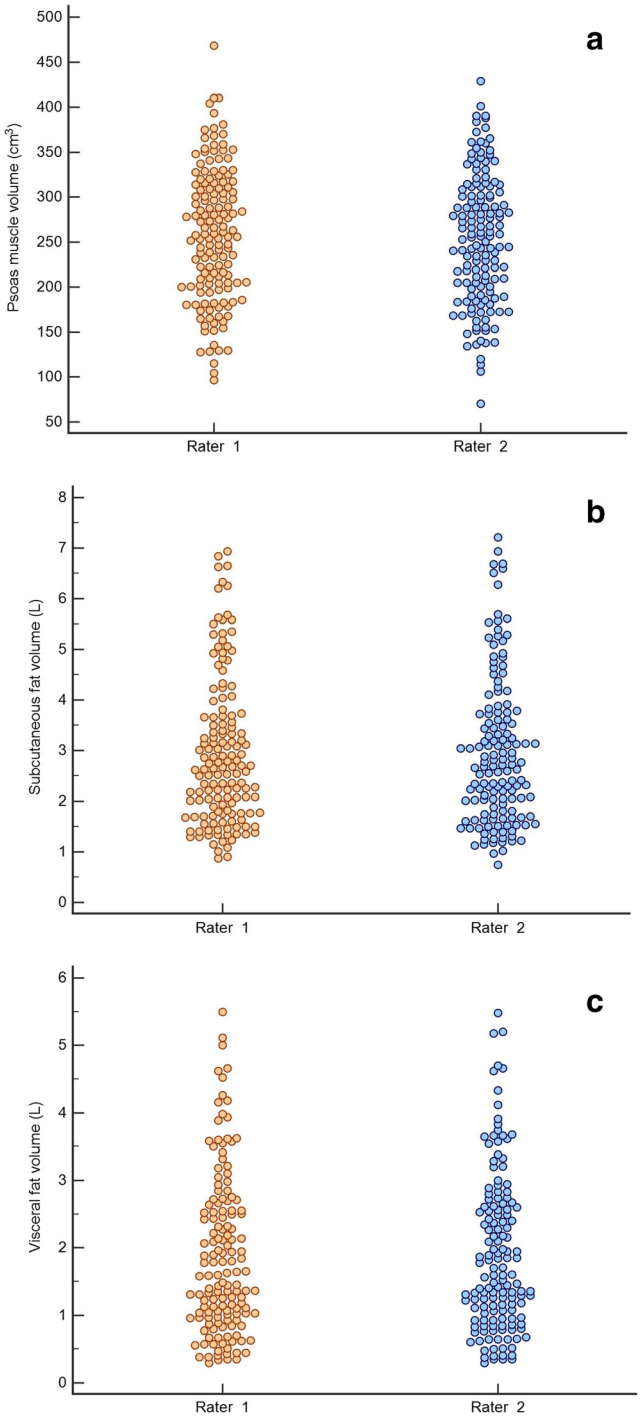


**Fig. 2** Measurements of psoas muscle volume (**a**), visceral fat volume (**b**), and subcutaneous fat volume (**c**) by two raters

evidenced by our finding of a significant inverse relationship between leptin and PMV (in all pancreatitis individuals altogether), consistently in all models. In particular, for every 1 ng/ml of leptin increase, a 57 $cm^3$ decrease in PMV was identified in the most adjusted model. Leptin, a 167 amino acid hormone mainly secreted by adipocytes, acts through specific leptin receptor (*LepR*) that belongs to the cytokine receptor class I family and is expressed in skeletal muscle (among other tissues) [39]. Our earlier studies showed that circulating levels of leptin are significantly and positively associated with persistent hyperglycaemia during the course of acute pancreatitis, as well as with abdominal adiposity during follow-up of individuals with acute pancreatitis [40]. While none of the previous studies on skeletal muscle size in diseases of the exocrine pancreas investigated leptin, a statistically significant inverse association between serum leptin and skeletal muscle size was

**Table 2** Differences in psoas mass size between the pancreatitis groups and healthy controls

| | FAP vs. healthy controls | | | RAP vs. healthy controls | | | CP vs. healthy controls | | | Progression of pancreatitis |
|---|---|---|---|---|---|---|---|---|---|---|
| | *β* | SE | *p* | *β* | SE | *p* | *β* | SE | *p* | *p* for trend |
| Psoas muscle volume | | | | | | | | | | |
| Model 1 | − 10.527 | 14.320 | 0.464 | −3.606 | 18.770 | 0.848 | − 23.101 | 25.135 | 0.360 | 0.480 |
| Model 2 | − 20.761 | 13.047 | 0.114 | − 21.750 | 17.137 | .207 | − 45.356 | 22.617 | *0.047* | *0.047* |
| Model 3 | − 32.427 | 13.572 | *0.018* | − 37.268 | 18.216 | *0.043* | − 68.563 | 23.927 | *0.005* | *0.005* |
| Model 4 | − 32.910 | 14.043 | *0.021* | − 40.069 | 18.720 | *0.034* | − 72.355 | 24.524 | *0.004* | *0.004* |
| Model 5 | − 42.407 | 14.320 | *0.004* | − 54.768 | 19.542 | *0.006* | − 93.849 | 24.928 | *< 0.001* | *< 0.001* |
| Psoas muscle index | | | | | | | | | | |
| Model 1 | − 6.917 | 4.135 | 0.097 | − 2.757 | 5.481 | 0.616 | − 13.029 | 7.390 | 0.080 | 0.151 |
| Model 2 | − 8.386 | 3.347 | *0.013* | − 6.623 | 4.454 | 0.139 | − 18.786 | 5.940 | *0.002* | *0.004* |
| Model 3 | − 7.748 | 3.678 | *0.037* | − 6.573 | 4.937 | 0.185 | − 17.702 | 6.484 | *0.007* | *0.018* |
| Model 4 | − 7.142 | 3.803 | 0.063 | − 6.624 | 5.069 | 0.194 | − 17.907 | 6.641 | *0.008* | *0.019* |
| Model 5 | − 10.268 | 3.912 | *0.010* | − 10.920 | 5.338 | *0.043* | − 21.590 | 6.810 | *0.002* | *0.004* |

Data are presented as $\beta$ coefficients (i.e. median difference in PMV or PMI between each pancreatitis group and healthy control group) and standard errors, from linear regression models. Data on progression of pancreatitis were derived from the regression analysis of PMV/PMI of the four study groups in the following order: healthy controls, FAP, RAP, and CP. Statistically significant ($p < 0.05$) differences are shown in italics

*FAP*, first episode of acute pancreatitis; *RAP*, recurrent acute pancreatitis; *CP*, chronic pancreatitis; *SE*, standard error

*Model 1*, unadjusted model; *Model 2*, adjusted for age and sex; *Model 3*, adjusted for age, sex, V/S ratio, and HbA1c; *Model 4*, adjusted for age, sex, V/S ratio, HbA1c, physical activity, and ACCI; *Model 5*, adjusted for age, sex, V/S ratio, HbA1c, physical activity, ACCI, pancreatic amylase, tobacco smoking status, and alcohol consumption

observed in the studies of elderly individuals and patients with osteoarthritis [41–43]. The involvement of leptin can be two-fold. The first mechanism is related to excess adiposity. Sarcopenic obesity, a syndrome that puts individuals at risk of synergistic complications from both sarcopenia and obesity, is becoming increasingly recognised [44]. In brief, overexpression of suppressors of cytokine signalling-3 in the liver impairs leptin signalling (specifically, the Janus kinase-2/signal

**Table 3** Associations between psoas mass size and the studied cytokines

| | IL-6 | | | TNFα | | | Leptin | | | CCL2 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *β* | SE | *p* | *β* | SE | *p* | *β* | SE | *p* | *β* | SE | *p* |
| Psoas muscle volume | | | | | | | | | | | | |
| Model 1 | − 0.0120 | 0.140 | .930 | − 0.363 | .833 | .664 | − 0.018 | 0.008 | *0.016* | 0.011 | 0.028 | 0.699 |
| Model 2 | − 0.013 | 0.126 | .373 | − 0.787 | .745 | .293 | − 0.015 | 0.007 | *0.035* | − 0.001 | 0.026 | 0.964 |
| Model 3 | − 0.137 | 0.657 | *0.025* | − 0.799 | .729 | .275 | − 0.016 | 0.007 | *0.022* | 0.003 | 0.025 | 0.915 |
| Model 4 | − 1.47 | 0.130 | .261 | − 0.898 | .756 | .237 | − 0.016 | 0.007 | *0.023* | 0.004 | 0.026 | 0.886 |
| Model 5 | − 1.49 | 0.133 | .264 | − 0.766 | .799 | .328 | − 0.16 | 0.007 | *0.030* | 0.000 | 0.027 | 0.994 |
| Psoas muscle index | | | | | | | | | | | | |
| Model 1 | 0.001 | 0.033 | .987 | 0.034 | .247 | .891 | − 0.005 | 0.002 | *0.020* | − 0.003 | 0.008 | 0.726 |
| Model 2 | 0.003 | 0.027 | .909 | − 0.73 | .201 | .716 | − 0.004 | 0.002 | *0.045* | − 0.004 | 0.007 | 0.607 |
| Model 3 | 0.003 | 0.033 | .937 | − 0.064 | .196 | .745 | − 0.003 | 0.002 | 0.060 | − 0.004 | 0.007 | 0.530 |
| Model 4 | − 0.008 | 0.035 | .828 | − 0.111 | .202 | .583 | − 0.004 | 0.002 | 0.054 | − 0.004 | 0.007 | 0.552 |
| Model 5 | − 0.08 | 0.035 | .811 | − 0.136 | .208 | .514 | − 0.004 | 0.002 | *0.044* | − 0.005 | 0.007 | 0.461 |

Data are presented as $\beta$ coefficients (i.e. median difference in PMV or PMI between the inflammatory markers) and standard errors, from linear regression models. Statistically significant ($p < 0.05$) differences are shown in italics

*IL-6*, interleukin-6; *TNFα*, tumour necrosis factor-α; *CCL2*, C-C motif chemokine ligand 2; *SE*, standard error

*Model 1*, unadjusted model; *Model 2*, adjusted for age and sex; *Model 3*, adjusted for age, sex, V/S ratio, and HbA1c; *Model 4*, adjusted for age, sex, V/S ratio, HbA1c, pancreatic amylase, physical activity, and ACCI; *Model 5*, adjusted for age, sex, V/S ratio, HbA1c, physical activity, ACCI, tobacco smoking status, and alcohol consumption

transducer and activator of the transcription-3 pathway), thereby inducing leptin resistance. Notably, the mean BMI of individuals following pancreatitis in the present study was 28.1 kg/m$^2$ and the visceral-to-subcutaneous fat volume ratio showed a steady increase from healthy controls (0.36) to FAP (0.69) to RAP (0.75) to CP (1.09) ($p < 0.001$). Second, leptin (indirectly) stimulates melanocortin-4 receptor signalling, which is classically known to suppress appetite in the brain [45]. Moreover, given the 2014 study that showed that melanocortin-4 receptor is also expressed in enteroendocrine L cells and the α-melanocyte-stimulating hormone (one of the main effectors of melanocortin-4 receptor) stimulates the release of glucagon-like peptide-1 and peptide YY from L cells [46], we hypothesise that hypersecretion of leptin influences gut hormones that are produced by enteroendocrine cells and released into the circulation. One way or another, hypersecretion of leptin decreases food consumption and this may result in reduced muscle size.

This study has several strengths. First, the measurement of PMV was in line with the previously published method [27]. In addition, the PMI was calculated to account for the variations in anthropometrics between the study participants [47]. The observed associations were consistent between PMV and PMI. Second, the protocol of MR-derived measurements was applied to all participants independently by two raters, blinded to the study group allocation and characteristics. The inter-rater reliability was excellent with ICCs of 0.98 for the PMV measurements and 0.99 for the VFV and SFV measurements. To the best of our knowledge, this is the only study on psoas muscle to have used two raters to measure its size in the entire study cohort. Third, the study was nested into prospective cohort study; hence, pancreatitis was diagnosed prospectively in all participants and the used definitions were in line with the international recommendations (as opposed to the use of hospital discharge codes, which are prone to misclassification bias [48]). Further, participants were followed up prospectively (including the development of repeated attacks of pancreatitis). Last, several covariates that are known to affect skeletal muscle size were accounted for. This included age, sex, physical activity level, smoking status, alcohol consumption, V/S fat volume ratio, comorbidities, markers of glucose metabolism, and exocrine pancreatic function [49, 50].

The study also has several limitations. We were not able to account for some of the covariates that may influence skeletal muscle size. Specifically, long-term use of corticosteroids results in muscle depletion [51]. However, people using corticosteroids were excluded from the study a priori. Further, serum levels of cortisol were not found to be involved in metabolic changes following pancreatitis in our earlier study [52]. The same study also showed no involvement of growth hormone, which stimulates insulin-like growth factor 1 (frequently found to be decreased in people with reduced skeletal muscle size). Malnutrition due to insufficient caloric intake is another known factor that contributes to skeletal muscle loss [53]. However, all patients with BMI < 18.5 were excluded from the study a priori. Vitamin D deficiency is another contributor for which we did not account for directly, though this deficiency is usually present in individuals with exocrine pancreatic dysfunction and we did account for the latter statistically (using pancreatic amylase as a proxy) [54]. Last, the study design was cross-sectional and, hence, no inference about causality can be made yet [55, 56]. While it is tempting to imply that the reduced psoas muscle size is the result of progression of pancreatitis, it is theoretically possible that individuals with lower psoas muscle size are more prone to progression of pancreatitis. A prospective longitudinal study is now warranted to address this issue unequivocally.

In conclusion, psoas muscle size is significantly lower in individuals after pancreatitis than healthy controls after adjusting for age, sex, body fat composition, and other covariates. Moreover, there is a progressive reduction in psoas muscle size from FAP to RAP to CP. Hypersecretion of leptin appears to be one of the factors behind this observation.

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## Compliance with ethical standards

**Guarantor** The scientific guarantor of this publication is Associate Professor Max Petrov, MD, MPH, PhD.

**Conflict of interest** The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

**Statistics and biometry** Two of the authors have significant statistical expertise.

**Informed consent** Written informed consent was obtained from all participants in this study.

**Ethical approval** Health and Disability Ethics Committee approval was obtained.

**Methodology**
- Prospective
- Cross-sectional study
- Performed at one institution

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