World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i34.4329

World J Gastroenterol 2010 September 14; 16(34): 4329-4334
ISSN 1007-9327 (print)

BRIEF ARTICLE

Associated factors for a hyperechogenic pancreas on endoscopic ultrasound

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Supported by A Grant of the Korea Healthcare technology R&D Project, Ministry of Health and Welfare, South Korea, (A091047)
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Received: March 1, 2010 Revised: May 4, 2010
Accepted: May 11, 2010
Published online: September 14, 2010

Abstract

AIM: To identify the associated risk factors for hyperechogenic pancreas (HP) which may be observed on endoscopic ultrasound (EUS) and to assess the relationship between HP and obesity.

METHODS: From January 2007 to December 2007, we prospectively enrolled 524 consecutive adults who were scheduled to undergo EUS. Patients with a history of pancreatic disease or with hepatobiliary or advanced gastrointestinal cancer were excluded. Finally, 284 patients were included in the analyses. We further analyzed the risk of HP according to the categories of visceral adipose tissue (VAT) and subcutaneous adipose tissue in 132 patients who underwent abdominal computed tomography scans.

RESULTS: On univariate analysis, age older than 60 years, obesity (body mass index > 25 kg/m^2), fatty liver, diabetes mellitus, hypertension and hypercholesterolemia were identified as risk factors associated with HP (P < 0.05). On multivariate analysis, fatty liver [P = 0.008, odds ratio (OR) = 2.219], male gender (P = 0.013, OR = 2.636), age older than 60 years (P = 0.001, OR = 2.874) and hypertension (P = 0.044, OR = 2.037) were significantly associated with HP. In the subgroup analysis, VAT was a statistically significant risk factor for HP (P = 0.010, OR = 5.665, lowest quartile *vs* highest quartile).

CONCLUSION: HP observed on EUS was associated with fatty liver, male gender, age older than 60 years, hypertension and VAT.

Key words: Endoscopic Ultrasound; Hyperechogenic pancreas; Obesity

Peer reviewers: Evangelos Kalaitzakis, MD, PhD, Associate Professor, Institute of Internal Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg 41345, Sweden; Tarkan Karakan, Associate Professor, Department of Gastroenterology, Gazi University, Ankara, 06500, Turkey

Choi CW, Kim GH, Kang DH, Kim HW, Kim DU, Heo J, Song GA, Park DY, Kim S. Associated factors for a hyperechogenic pancreas on endoscopic ultrasound. *World J Gastroenterol* 2010; 16(34): 4329-4334 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i34/4329.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i34.4329

INTRODUCTION

Endoscopic ultrasound (EUS) has been an important tool for diagnosing gastrointestinal and pancreatobiliary disease since the 1980s[1]. EUS is particularly effective for evaluating patients with pancreatic disease, because EUS provides high resolution images of the pancreatic duct as well as the parenchyma. In recent years, EUS-guided fine-needle aspiration or trucut biopsy can be performed at the same time and this procedure enables tissue diagnosis.

Identification of hyperechogenic pancreas (HP) is not uncommon during EUS. However, the clinical significance of HP is still unclear. Fatty liver is associated with insulin resistance, dyslipidemia and obesity (especially central body fat distribution) and is considered a phenotype of metabolic syndrome[2-4]. Visceral fat is more important for metabolic syndrome and hepatic steatosis than subcutaneous fat owing to its steatogenesis and production of various cytokines[5,6]. The normal pancreatic echogenicity on ultrasound is equal to or slightly greater than that of the liver[7,8]. Pancreatic echogenicity is determined by fat deposited around the pancreas and within the septa transversing the normal pancreas[9]. However, the role of obesity as a risk factor for HP remains unclear. We hypothesized that HP is related to obesity in a similar way to its relationship with fatty liver. Many different methods have been used to quantify obesity, such as body mass index (BMI), waist circumference, waist-to-hip ratio, skin fold thickness and percentage of body fat. Among these methods, computed tomography (CT) is considered the gold standard not only for evaluating adipose tissue, but also for multi-compartment body measurements[10].

The aim of this study was to determine the incidence of HP in patients undergoing EUS and to identify the associated risk factors for HP on EUS.

MATERIALS AND METHODS

From January 2007 to December 2007, a total of 524 patients who underwent EUS were prospectively enrolled in the study. Pancreatic disease can alter the sonographic appearance of the pancreas, therefore patients with a history of or who showed the presence of pancreatic disease such as chronic pancreatitis were excluded (n = 156), and patients with hepatobiliary or advanced gastrointestinal cancer were also excluded from the study (n = 84). Finally, a total of 284 patients were included (Figure 1) and all EUS examinations were performed to evaluate subepithelial tumors. EUS examinations were performed using a radial echoendoscope (Olympus GF-UM2000 with 5 MHz and 7.5 MHz frequency transducers) by a single experienced endoscopist (Kim GH). Informed consent was obtained after the patients were given a complete description of the study. All the patients completed a questionnaire regarding their personal medical history, including alcohol intake and smoking. This study was approved by the Ethics Committee of Pusan National University Hospital.

During the study, we measured the levels of serum pancreatic enzymes, took clinical histories, conducted physical examinations, and performed blood analyses including blood sugar, total cholesterol and liver function tests. The degree of echogenicity of the pancreas was judged relative to the liver (or the kidney if the liver was hyperechogenic) (Figure 2). The patients' histories of alcohol consumption were obtained, and the term "nonalcoholic" was applied to men who consumed less than 30 g alcohol/d and to women who consumed less than 20 g alcohol/d. We further analyzed the risk of HP according to the categories of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) in 132 patients who underwent abdominal CT scanning for clinical purposes.

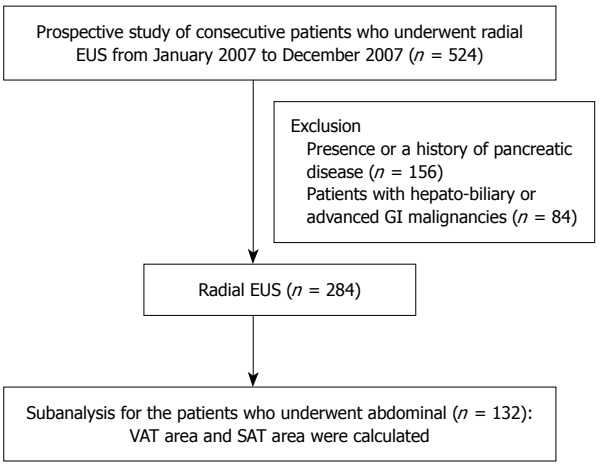

Figure 1 Flow chart indicating the progression from the initial assessment when first referred for endoscopic ultrasound to the final analysis. EUS: Endoscopic ultrasound; GI: Gastrointestinal; VAT: Visceral adipose tissue; SAT: Subcutaneous adipose tissue.

Laboratory investigations and assessment of the abdominal visceral fat area

The clinical characteristics of all subjects were prospectively evaluated, including gender, age, systolic blood pressure, diastolic blood pressure, BMI and routine blood values. These parameters were measured within 30 d of EUS. Hypertension was defined as systolic BP $\geq$ 140 mmHg or diastolic BP $\geq$ 90 mmHg[11]. Type 2 diabetes mellitus (DM) was defined as a fasting plasma glucose level $\geq$ 126 mg/dL or if there were symptoms of hyperglycemia and the random venous plasma glucose level was $\geq$ 200 mg/dL[12]. Hypercholesterolemia was defined when the serum total cholesterol level was above the reference value (more than 240 mg/dL at our hospital). The body mass index (BMI) was calculated as the body weight (kg) divided by the square of the standing height (m). The BMI was categorized into three levels according to the WHO criteria for the Western Pacific region[13]: normal weight-BMI < 23 kg/m^2, overweight-BMI $\geq$ 23 kg/m^2 and $\leq$ 25 kg/m^2 and obese-BMI > 25 kg/m^2. To determine the VAT and SAT on CT scans, adipose tissue area was calculated at the level of the umbilicus, with an attenuation that ranged from -50 to -250 Hounsfield units[2,14]. The subjects were examined in the supine position. The VAT was defined as intra-abdominal fat bound by the pa-

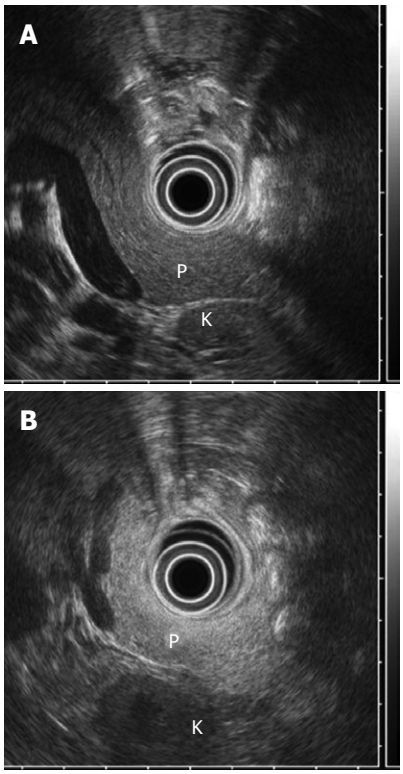

Figure 2 Echogenicity of the pancreas on endoscopic ultrasound. A: Normal echogenic pancreas; B: Hyperechogenic pancreas compared to kidney. P: Pancreas; K: Kidney.

rietal peritoneum or the transversalis fascia excluding the vertebral column and the para-spinal muscles, and the SAT was defined as fat superficial to the abdominal and back muscles. Using a cursor, the VAT was measured around the inner boundary of the abdominal wall muscles. A region of interest drawn around the external margin of the dermis was used to calculate the area of total adipose tissue (TAT). SAT was obtained by subtracting the VAT from the TAT (Figure 3)[2,15].

Statistical analysis

The data were expressed as means ± SD. The unpaired *t*-tests were used to compare the mean values of the characteristics between the HP group and the non-HP group. χ^2 tests were used for the nominal variables. Variables with a *P* value less than 0.25 on univariate analysis were included in a forward stepwise multiple logistic regression model. To detect the dose-response relationship, we used cut-off points to categorize the patients into quartiles for the SAT and VAT. Logistic regression analysis was used to estimate the crude and adjusted strength of the association between the positive and negative HP groups. All data analyses were performed using SPSS for Windows version 12.0 (SPSS, Chicago, IL, USA). A *P*-value less than 0.05 was considered significant.

RESULTS

Baseline characteristics of the study sample

The total number of subjects included was 284 (102 males and 182 females) and their mean age was 52.1 ± 12.2 years. Among the study subjects who underwent EUS, 11 were HP patients (38.7%). Thirty-four patients (33.1%) had fatty livers. There were 70 (24.6%) current smokers and 106 (37.3%) alcohol drinking patients. The mean BMI was 23.1 ± 2.9 kg/m^2. Among the 132 patients who underwent an abdominal CT scan, the mean SAT and VAT were 145.6 ± 49.3 and 71.7 ± 43.6 cm^2, respectively (Table 1).

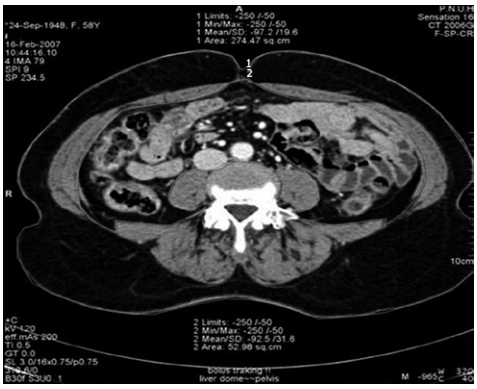

Figure 3 Calculation of the abdominal adipose tissue distribution using computed tomography scans. The total adipose tissue (TAT) area was obtained by applying an adipose tissue threshold to a region of interest (ROI) that was traced around the dermis (1). An ROI was traced around the inner margin of the abdominal wall muscles, and an adipose tissue threshold was applied to determine the area of visceral adipose tissue (VAT) in the ROI (2). The subcutaneous adipose tissue area was then obtained by subtracting the VAT from the TAT.

Table 1 Baseline characteristics of the study population (mean ± SD) *n* (%)

	Total patients (*n* = 284)
Gender (M:F)	102:182
Age (yr)	52.1 ± 12.2
Hyperechogenic pancreas positive	110 (38.7)
Current cigarette smoking	70 (24.6)
Current alcohol drinking	106 (37.3)
Hypertension (≥ 140/90 mmHg)	61 (21.5)
BMI (kg/m^2)	23.1 ± 2.9
Fatty liver	94 (33.1)
Diabetes mellitus	46 (16.2)
Hypercholesterolemia	46 (16.1)
CT measurement (*n* = 132)	
SAT area (cm^2)	145.6 ± 49.3
VAT area (cm^2)	71.7 ± 43.6

BMI: Body mass index; CT: Computed tomography; SAT: Subcutaneous adipose tissue; VAT: Visceral adipose tissue.

Comparison of patients with and without hyperechogenic pancreas

We analyzed the potential risk factors for HP. On univariate analysis, age older than 60 years, obesity (BMI more than 25 kg/m^2), fatty liver, type 2 DM, hypertension and hypercholesterolemia were the associated risk factors for HP ($P < 0.05$) (Table 2). On multivariate analysis, fatty liver [$P = 0.008$, odds ratio (OR) = 2.219], male gender ($P = 0.013$, OR = 2.636), age older than 60 years ($P = 0.001$, OR = 2.874) and hypertension ($P = 0.044$, OR = 2.037) were the significant associated risk factors for HP (Table 3).

Table 2 Comparison between the patients with and without hyperechogenic pancreas (mean ± SD) *n* (%)

	HP negative (*n* = 174)	HP positive (n = 110)	*P* value
Age (yr)	48.9 ± 12.0	57.2 ± 10.7	< 0.001
Male gender	69 (39.9)	33 (30.0)	0.099
BMI (kg/m^2)	22.4 ± 2.8	24.0 ± 2.7	< 0.001
Smoking	47 (27.0)	23 (20.9)	0.245
Alcohol	71 (40.8)	35 (31.8)	0.127
Type 2 DM	7 (4.0)	12 (10.9)	0.024
Hypertension	25 (14.4)	36 (32.7)	< 0.001
Hypercholesterolemia	20 (11.5)	26 (23.6)	0.007
Fatty liver	46 (26.4)	48 (43.6)	0.003

HP: Hyperechogenic pancreas; BMI: Body mass index; DM: Diabetes mellitus.

Table 3 Multivariate analysis of the clinical risk factors for hyperechogenic pancreas

	P value	OR	95% CI
Male gender	0.013	2.636	1.224-5.678
Age older than 60 yr	0.001	2.874	1.537-5.372
Obesity (BMI > 25 kg/m^2)	0.439	1.296	0.673-2.496
Smoking	0.612	1.227	0.557-2.701
Alcohol	0.435	0.773	0.405-1.475
Type 2 DM	0.646	1.304	0.420-4.055
Hypertension	0.044	2.037	1.018-4.072
Hypercholesterolemia	0.099	1.821	0.893-3.713
Fatty liver	0.008	2.219	1.226-4.016

BMI: Body mass index; DM: Diabetes mellitus; OR: Odds ratio; CI: Confidence interval.

A subanalysis was performed in patients who underwent abdominal CT (n = 132). On univariate analysis, VAT and SAT were significantly different between the groups (89.5 ± 47.8 cm^2 *vs* 59.8 ± 36.3 cm^2, respectively, P < 0.001 for VAT and 162.2 ± 55.7 cm^2 *vs* 134.5 ± 59.3 cm^2, respectively, P = 0.008 for SAT) (Table 4). On multivariate analysis, for patients who underwent abdominal CT, VAT was a statistically significant risk factor for HP after adjusting for age, gender, alcohol, smoking and BMI (P = 0.010, OR = 5.665, the lowest quartile *vs* the highest quartile) (Table 5).

DISCUSSION

EUS represents a major advance in gastrointestinal imaging technology. EUS of the pancreas is particularly useful, because the pancreas can be visualized either from the duodenum or from the stomach. EUS is less risky than endoscopic retrograde pancreatography, which is the traditional imaging test of choice and the gold standard for diagnosing chronic pancreatitis[16,17]. Having an understanding of the normal variations in the pancreatic parenchyma is crucial when evaluating pancreatic abnormalities. HP is not an infrequent finding during EUS, but the clinical significance of hyperechogenicity of the normal pancreas is not known. In this study, pancreatic echogenicity was compared with liver echogenicity to evaluate fat deposition in the pancreas. However, in fatty liver, liver echogenicity is not a good reference value for HP. Therefore, we used kidney parenchymal echogenicity if fatty liver was present[18]. A very high echogenicity of the pancreas could be a sign of chronic pancreatitis, which is often accompanied by dilatation of the pancreatic duct. A previous study showed that body weight and fatty infiltration have a significant influence on pancreatic echogenicity[19]. Hepatic steatosis (or fatty liver) is associated with obesity, old age, hyperlipidemia, hyperglycemia and hypertension[2,3,5]. Visceral adiposity is known to be more important than BMI for predicting the presence of hepatic steatosis[5].

Table 4 Comparison of adipose tissue between patients with and without hyperechogenic pancreas *n* (%)

	HP negative (*n* = 79)	HP positive (*n* = 53)	*P* value
VAT area (cm^2)			< 0.001
Quartile Ⅰ (< 35.2)	23 (29.1)	9 (17.0)	
Quartile Ⅱ (35.2-65.9)	25 (31.6)	8 (15.1)	
Quartile Ⅲ (65.9-94.0)	19 (24.1)	14 (26.4)	
Quartile Ⅳ (> 94.0)	12 (15.2)	22 (41.5)	
SAT area (cm^2)			0.008
Quartile Ⅰ (< 109.3)	24 (30.4)	9 (17.0)	
Quartile Ⅱ (109.3-139.7)	22 (27.8)	11 (20.8)	
Quartile Ⅲ (139.7-179.2)	18 (22.8)	16 (30.2)	
Quartile Ⅳ (> 179.2)	15 (19.0)	17 (32.1)	

HP: Hyperechogenic pancreas; VAT: Visceral adipose tissue; SAT: Subcutaneous adipose tissue.

At first, we assumed that HP in an otherwise normal pancreas would be associated with fatty liver and its associated risk factors, especially obesity. On multivariate analysis, fatty liver, age older than 60 years, male gender and hypertension were the significant risk factors for HP. The pancreas in older patients showed different changes, such as atrophy, fibrosis and fatty infiltration. A previous histopathologic study showed that after the age of 60 years, moderate to severe fat accumulation is typically evident in the acinar cells of the pancreas[20]. High echogenicity of the pancreas is a normal finding in older patients[21]. Another previous EUS study of the age-related changes of the pancreas showed that men had significantly greater odds for having abnormalities than did women (OR = 2.9, P = 0.01)[22]. Because the distribution of abdominal fat differs according to gender, the areas of subcutaneous fat are significantly greater in women than in men at the abdominal level[23-25]. Metabolic syndrome is more prevalent in men than in women up to the age of 60 and this is closely related to hepatic steatosis; our results may reflect such a profile[26,27].

Hepatic steatosis is usually prevalent in obese subjects and regional fat distribution associated with insulin resistance was found to be an important factor for hepatic steatosis in several studies[28]. The BMI reflects either the total body fat accumulation or the subcutaneous fat accumulation. Recent findings have shown that central obesity (visceral fat accumulation) may be a more important factor for hepatic steatosis than BMI[29]. CT is considered the gold standard not only for measuring adipose tissue, but also

Table 5 Multivariable analysis: Unadjusted and adjusted analyses for the relationships of the abdominal adipose tissue area with hyperechogenic pancreas, OR (95% CI)

	Unadjusted analysis	*P* value	Adjusted analysis[1]	*P* value
VAT area (cm^2)		0.015		0.010
Quartile Ⅰ (< 35.2)	Reference		Reference	
Quartile Ⅱ (35.2-65.9)	0.646 (0.202-2.059)		0.671 (0.214-2.365)	
Quartile Ⅲ (65.9-94.0)	1.311 (0.637-6.094)		1.997 (0.561-7.107)	
Quartile Ⅳ (> 94.0)	3.491(1.154-10.557)		5.665 (1.515-21.180)	
SAT area (cm^2)		0.414		0.960
Quartile Ⅰ (< 109.3)	Reference		Reference	
Quartile Ⅱ (109.3-139.7)	1.139 (0.374-3.471)		1.016 (0.316-3.271)	
Quartile Ⅲ (139.7-179.2)	1.97 (0.637-6.094)		1.353 (0.378-4.841)	
Quartile Ⅳ (> 179.2)	2.288 (0.720-7.268)		1.227 (0.301-4.992)	

[1]Adjusted for age, gender, smoking, alcohol, body mass index. VAT: Visceral adipose tissue; SAT: Subcutaneous adipose tissue; OR: Odds ratio; CI: Confidence interval.

for performing multi-compartment body measurements[10]. Even so, there have been few studies on the relationship between HP and regional fat distribution as measured by CT. We performed a subgroup analysis on patients who underwent abdominal CT. This objective measure of visceral fat showed that VAT was an independent risk factor for HP after adjusting for age, gender, alcohol, smoking and BMI. Obesity is known to be accompanied by metabolic complications and is increasingly recognized as a risk factor for type 2 DM, dyslipidemia, atherosclerotic and cardiovascular disease. There is growing evidence that the regional distribution of adipose tissue appears to be an important indicator of metabolic and cardiovascular alterations, since only inconstant correlations between BMI and these disturbances have been found[30]. On multivariate analysis in the present study, although BMI was not a statistically significant risk factor, VAT was an independent, significant risk factor for HP. A possible reason for this is that VAT measured by CT scanning is more accurate for measuring visceral obesity than BMI[31].

Recently, two studies regarding fatty pancreas or hyperechogenic pancreas were reported[18,32]. In one study, the predictors of HP were found to be hepatic steatosis, alcohol use and increased BMI[32]. In the other study, fatty pancreas was associated with metabolic syndrome. In the latter study, visceral fat was also independently associated with fatty pancreas[18]. However, that study simply compared VAT area values between fatty pancreas and normal controls. In the present study, we subdivided SAT and VAT area into four quartiles to evaluate the relationship between adipose tissue area and HP.

In the present study, alcohol intake and cigarette smoking were not significant risk factors for HP. Another study has suggested that alcohol consumption and cigarette smoking affect the endosonographic appearance of the pancreas in a dose-dependent fashion[33]. Although an effort was made to gather precise information on drinking and smoking in our sample, underestimation of alcohol intake and cigarette smoking may explain this finding in our study.

Although we performed this study prospectively, there were some limitations. First, the control group (non-HP group) was not representative of the general healthy population because the sample was made up of patients who required EUS for the evaluation of a subepithelial tumor. Second, direct determination of the pancreatic fat and visceral fat in tissue was not conducted. Due to ethical considerations with regard to obtaining tissue specimens from disease-free subjects, we did not perform tissue biopsies. Third, quantitative analyses of the pancreatic parenchymal echogenicity were not performed. As we only compared pancreatic echogenicity with echogenicity of the liver or kidney, these comparisons might have been somewhat subjective. A future study that employs computer-assisted quantitative analysis may be warranted.

In conclusion, HP is correlated with hepatic steatosis, hypertension, male gender and age older than 60 years. VAT is positively correlated with HP regardless of BMI. Although it is unknown whether HP is a progressive condition, HP, and likewise fatty liver, may be one of the phenotypes of metabolic syndrome, which is characterized by obesity with visceral fat accumulation, DM, hyperlipidemia and hypertension. Further studies are needed to confirm this hypothesis.

COMMENTS

Background

A hyperechogenic pancreas (HP) is commonly found during endoscopic ultrasound (EUS). However, the clinical significance of HP is still unclear. Visceral fat is more important for metabolic syndrome and hepatic steatosis than subcutaneous fat owing to its steatogenesis and production of various cytokines. Pancreatic echogenicity is determined by fat deposited around the pancreas and within the septa transversing the normal pancreas. Yet the role of obesity as a risk factor for HP is unclear. The authors could assume that HP is related to obesity in a similar way to that of fatty liver.

Research frontiers

HP may is related to obesity in a similar way to that of fatty liver. Many different methods have been used to calculate a value for obesity, such as body mass index (BMI), waist circumference, waist-to-hip ratio, skin fold thickness and percentage of body fat. Among these methods, computed tomography is considered the gold standard not only for evaluating adipose tissue, but also for multi-compartment body measurements.

Innovations and breakthroughs

HP is correlated with hepatic steatosis, hypertension, male gender and age older than 60 years. Visceral adipose tissue is positively correlated with HP regardless of BMI.

Applications

Although it is unknown whether HP is a progressive condition, HP, and likewise fatty liver, may be one of the phenotypes for metabolic syndrome, which is characterized by obesity with visceral fat accumulation, diabetes mellitus, hyperlipidemia and hypertension.

Terminology

Hyperechogenic pancreas was observed when the degree of echogenicity of the pancreas relative to the liver (or the kidney if the liver was hyperechogenic) was higher.

Peer review

Choi *et al* have performed a prospective study in order to identify factors related to hyperechogenic pancreas on EUS. This is an interesting study as published data on "fatty" pancreas are not extensive.

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