—Review Article—

Pancreatic changes with lifestyle and age: What is normal and what is concerning?

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ABSTRACT

During the aging process, typical morphological changes occur in the pancreas, which leads to a specific "patchy lobular fibrosis in the elderly." The aging process in the pancreas is associated with changes in volume, dimensions, contour, and increasing intrapancreatic fat deposition. Typical changes are seen in ultrasonography, computed tomography, endosonography, and magnetic resonance imaging. Typical age-related changes must be distinguished from lifestyle-related changes. Obesity, high body mass index, and metabolic syndrome also lead to fatty infiltration of the pancreas. In the present article, age-related changes in morphology and imaging are discussed. Particular attention is given to the sonographic verification of fatty infiltration of the pancreas. Ultrasonography is a widely used screening examination method. It is important to acknowledge the features of the normal aging processes and not to interpret them as pathological findings. Reference is made to the uneven fatty infiltration of the pancreas. The differential diagnostic and the differentiation from other processes and diseases leading to fatty infiltration of the pancreas are discussed.

Key words: Age, fat deposition, pancreatic echogenicity, pancreatic parenchyma

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INTRODUCTION

The pancreas undergoes an aging process with various morphological changes. Autopsy studies have reported that with advancing age fibrosis and lipomatosis occur in the pancreas, ductal epithelial changes are present, and the pancreatic duct may be wider than in younger individuals.[1-3] Olsen[2] and Stamm[1] described a positive correlation between age and pancreatic lipomatosis.[1,2] In contrast, the weight of the pancreas decreases continuously from the age of 40 until advanced age. Pancreatic volume reaches a maximal mean value of 78.85 cm^3 in the third decade of life. According to this, the volume of the pancreas decreases significantly with increasing age, it shrinks at the age of 70–80 years to only 57.35 cm^3.[1]

As a result, the anteroposterior (AP) diameter of the pancreas and parenchymal volume decrease, while the fat volume increases. This is caused by the development of pancreatic parenchymal atrophy, fat infiltration, and intra-and perilobular fibrosis. At the same time, the pancreatic duct becomes slightly more prominent. The clinical significance of these changes is a matter of debate. Although these morphological age changes are not accompanied by symptoms, limitations of exocrine as well as endocrine pancreatic functions can be detected in a relevant number of affected elderly people. In 11.5% of the 50–75 years old, the fecal elastase is below 200 μg/g and in 5.1%, there is severe exocrine pancreatic insufficiency with fecal elastase <100 μg/g.[4,5] Dyspeptic complaints in the elderly are sometimes due to exocrine pancreatic insufficiency.[5] These data are confirmed in a study of >1000 participants with gastrointestinal symptoms but no known pancreatic disease. Among those over 70 years of age, 10% had fecal elastase <200 μg/g and 5% of <100 μg/g.[6] These results suggest that pancreatic enzyme secretion and function are impaired by age-related changes in healthy elderly people without underlying gastrointestinal diseases.[7] The endocrine function of the pancreas can also be impaired due to age. Both the basic secretory function and the glucose-stimulated secretory function of the islet cells decline with age.[5]

Fatty degeneration of the pancreas is a common process during aging. Several other conditions are associated with a fatty pancreas, including overweight/obesity, high body mass index (BMI), hypercholesterolemia, type 2 diabetes, arterial hypertension, metabolic syndrome, and severe atherosclerosis. These are additional factors that can intensify age-related fatty infiltration of the pancreas. The impact of diabetes mellitus type 2 is discussed contradictorily.[8-10] It raises the interesting question of whether the aging process is an independent factor in pancreatic fat infiltration.

There are also age-related neoplastic changes in the pancreas. These include the increasing frequency of pancreatic intraepithelial neoplasia (PanIN) with advancing age in people over 40 years of age.[11]

The aging pancreas may still have compensatory capabilities, but the other metabolic factors and Western lifestyle may lead to further impairment.

The following article focuses on age-related changes of the pancreatic parenchyma in imaging, especially in abdominal ultrasonography.

AGE-RELATED MORPHOLOGICAL CHANGES

The "normal" pancreas without pancreatic diseases develops a specific type of fibrosis that is highly age dependent. Schmitz-Moormann *et al.*[3] found significant correlations between ductal epithelial hyperplasia, intralobular fibrosis and perilobular fibrosis, and age. These age-dependent pancreatic changes are thought to begin with intraductal epithelial proliferation, followed by intralobular and perilobular fibrosis.[3]

In an autopsy study of Detlefsen *et al.*,[12] fibrotic changes were significantly more common in individuals over 60 years of age. Persons whose ages ranged from 20 to 59 only rarely exhibited pancreatic fibrosis. The probability of pancreatic fibrosis in groups <60 years old and ≥60 years old was 10.3% and 62.0%, respectively. Normal pancreatic tissues from 60-to 86-year-old subjects frequently showed focal lobular fibrosis. These fibrotic foci occurred in the periphery of the glands and involved one or two lobules where the acinar cells were replaced by connective tissue. Fibrotic foci were commonly associated with ductal papillary hyperplasia. 60-to 86-year-old subjects frequently showed PanIN-1B lesions (62.0%). In these persons, the PanIN-1B lesions were more common in or near to fibrotic lobuli (80.6%) than in pancreatic lobuli unaffected by fibrosis. The association between PanIN-1B and fibrosis was statistically significant ($P < 0.002$).[12] Since most pancreatic organs

had more than one fibrotic focus, the fibrosis pattern was that of multifocal intralobular fibrosis, which the authors termed "patchy lobular fibrosis in the elderly." In addition, fibrosis-related ductal papillary hyperplasia could be found in individuals over 60 years old.

Detlefsen *et al.* demonstrated that fibrosis in the normal pancreas has a patchy distribution with a lobular pattern and a clear relationship to age and to duct narrowing due to epithelial hyperplasia.[12]

Stamm[1] observed in an autopsy study a clear progression of lipomatosis with the age of the patients. The average age of the patients without any detectable fat replacement was 21 years. The average age of the group with fat replacement of less than a quarter of the pancreas was 61.4 years. Stamm describes patchy intralobular or perilobular areas of fat replacement in these cases. The average age of the patients with lipomatosis was 73 years, referring to the cases, in which the adipose tissue had replaced more than a quarter of the parenchyma.[1]

The fatty infiltration of the pancreas is different from that of the liver. In fatty liver disease, the fat accumulates in the hepatocytes. Pancreatic steatosis is histologically characterized by an increased number of adipocytes. From a histopathological point of view, adipocytes infiltrate the pancreatic parenchyma scattered (intralobular fat) and/or accumulate in the perilobular space; this pattern is mainly observed around large vessels (interlobular fat). Both types of fatty degeneration may occur separately or together.[13]

Not only age but also diabetes mellitus type 2, generalized atherosclerosis,[1] and obesity[2] are factors that correlated with lipomatosis of the pancreas.[1,2] On the other hand, no significant association was found between obesity and lipomatosis of the pancreas in the autopsy study of Stamm,[1] and only one of nine chronic alcoholics showed pancreatic lipomatosis.[1] Another histopathological study showed moderate-to-severe fat accumulation in the pancreatic acinar cells in patients with excessive alcohol use after the age of 60. Toxic metabolic mechanism is a likely pathogenetic factor for these effects.[14]

A study using dynamic computed tomography (CT) showed a negative correlation between parenchymal perfusion of the normal human pancreas and the patient's age.[15]

The pathophysiological mechanisms of pancreatic lipomatosis and fibrosis are not well understood. There are some data suggesting that age-related atherosclerosis and decreased perfusion of the pancreas is the cause of fibrosis. Ammann defined the term "idiopathic senile chronic pancreatitis" (ISCP) which seems to be a particular form of chronic pancreatitis caused mainly by small vessel atherosclerotic disease. ISCP is characterized by advanced age at the time of first manifestation (95% over 50 years), a prevalence of males (81%), a high incidence of calcifications (60%), and a rather benign, often painless course (74%). There is a high incidence of signs of arteriopathy associated with ISCP. Arteritis of the lower limbs and/or coronary heart disease was detected in 42%.[16-18]

TERMINOLOGY OF INTRAPANCREATIC FAT DEPOSITION IN THE PANCREATIC PARENCHYMA

A variety of terms are used to describe intrapancreatic fat deposition (IPFD) in the pancreas[19,20] [Table 1]: IPFD, pancreatic lipomatosis, pancreatic steatosis, and fatty pancreas are common descriptive terms and can be used synonymously. Fat accumulation associated with obesity and metabolic syndrome has been defined as "fatty infiltration" or "nonalcoholic fatty pancreatic disease" (NAFPD). Based on predominantly animal experimental data and correlations with negative outcome parameters observed in cohort studies, these terms appreciate IPFD to be part of a pathological process induced by an abnormal adipokine milieu including reduced adiponectin and markedly elevated leptin.[21] This seems to be associated with increased infiltration of pancreatic parenchyma by monocytes and macrophages which produce proinflammatory cytokines that alter organ function. It is hypothesized that the accumulated fat leads to inflammation within the islet cells of the pancreas as well as to parenchymal fibrosis of the exocrine pancreas[22] and to pancreatic carcinogenesis.[23] This hypothesis is reflected by the term "nonalcoholic steatopancreatitis" (NASP) which corresponds to subclinical chronic pancreatitis owing to pancreatic fat accumulation.

Risk factors for the development of NAFPD are obesity, increasing age, male gender, dyslipidemia, alcohol abuse, arterial hypertension, and hyperferritinemia.[10,20,24] The extent of pancreatic fatty infiltration depends on the patient's waist

circumference.[10] However, there are controversial data regarding the relationship between type 2 diabetes mellitus and pancreatic fatty infiltration.[8-10] Hepatic steatosis is the strongest predictor for fatty pancreas[24] [Figure 1].

The term "fatty replacement" describes a special phenomenon caused by the death of the acinar cells and their replacement by fatty tissue [Figure 2]. Risk factors for developing focal fatty replacement are alcohol abuse, viral infections with retroviruses, iron overload in hereditary hemochromatosis or transfusion-related iron overload, and medications (corticosteroids, gemcitabine, octreotide, and rosiglitazone). Some congenital diseases are associated with focal fatty replacement such as cystic fibrosis, Shwachman–Diamond syndrome or Shwachman–Bodian–Diamond syndrome, and Johanson–Blizzard syndrome.[20]

Focal fatty infiltration (FFI) corresponds to focal fatty islands in the pancreatic parenchyma. It usually has irregular margins. The pancreatic duct and bile duct are not affected. There is no mass effect. FFI of the pancreas can be focal or partly diffuse. The anterior part of the pancreatic head is usually more affected. The posterior part of the pancreatic head and the processus uncinatus of the pancreas are mostly spared from fatty infiltration. FFI of the pancreas is usually hyperechoic on abdominal ultrasonography. However, it may be hypoechoic to the normal pancreas. On CT, FFI appears as a heterogeneous, poorly defined, hypodense lesion with a negative CT density value. In the postcontrast sections, the enhancement is low due to the islands of normally interposed parenchyma.[25]

Yang *et al.*[26] described the magnetic resonance imaging (MRI) appearance of FFI based on a case report: On in-phase T1-weighted images, the signal intensity of the mass was like the signal intensity of normal pancreatic parenchyma. On opposed-phase T1-weighted images, the signal intensity of the mass was significantly reduced compared to the in-phase MR images. On the T2-weighted images, the mass was not visible.[26] FFI may reflect that the process of fatty infiltration often starts focally.

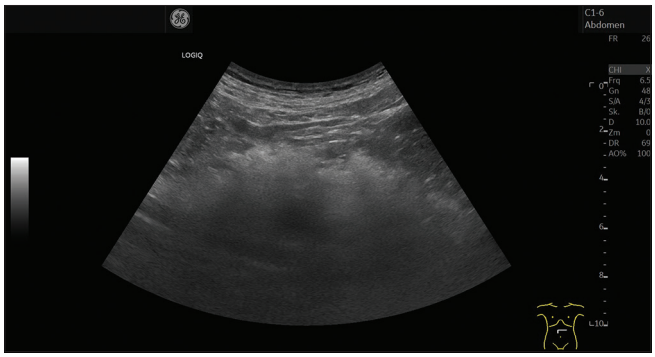

Figure 1. 60-year-old male. Metabolic syndrome. BMI 34. The pancreas is intensely hyperechoic on ultrasonography. The contour is lobulated. Severe fatty infiltration results in dorsal acoustic cancellation. BMI: Body mass index

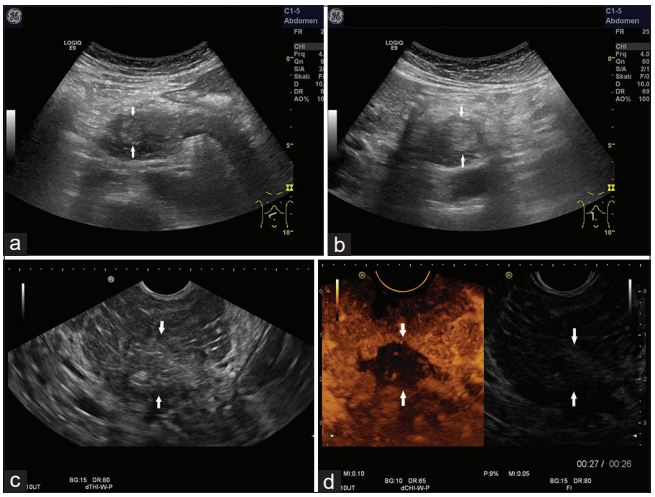

Figure 2. 56-year-old male. Focal fatty replacement. History of acute pancreatitis, continued alcohol abuse. Ultrasonography shows a focal hyperechoic area in the pancreatic head (a and b). On endosonography, this is irregularly delineated (c). In CELMI-EUS with 4.8 mL SonoVue the area is not enhanced (d). CELMI-EUS: Contrast-enhanced low mechanical index-EUS

Table 1. Terminology describing fat accumulation in the pancreas

Terms	Definition
IPFD Pancreatic lipomatosis/steatosis Fatty pancreas	Nonspecific terms describing fat accumulation within the pancreas; can be used synonymously
Lipomatous pseudohypertrophy	Describes an extreme variant of fat accumulation within the pancreas
Fatty parenchymal replacement	Includes a pathological process of acinar cell destruction and replacement (infiltration) by adipocytes, caused by exogenous noxes and iron deposits
Fatty pancreatic infiltration	Pancreatic infiltration by adipocytes in obesity and type 2 diabetes
NAFPD	Pancreatic fat accumulation in obesity and metabolic syndrome, the terms intend to classify this to be a pathological process
NASP	(Subclinical) pancreatitis due to fat accumulation in the pancreatic parenchyma

IPFD: Intrapancreatic fat deposition; NAFPD: Nonalcoholic fatty pancreatic disease; NASP: Nonalcoholic steatopancreatitis

Pancreatic lipomas are very rare, small, homogenous, and usually well-circumscribed pancreatic tumors. Some lipomas are hypoechogenic,[27] this can make it difficult to distinguish them from solid pancreatic tumors. In this case, the detection of fatty tissue on CT and MR scans is helpful. The diagnostic problem may be the differentiation between pancreatic lipoma and the FFI of the pancreas [Figures 3 and 4]. Both lesions usually have a density (CT) and signal intensity (MR) typical of fatty tissue. FFI of the pancreas is a heterogeneous lesion with poorly defined margins and visible but weak, nonhomogeneous contrast enhancement MRI is very helpful for the differentiation between FFI and lipoma. FFI is distinctly reduced on opposed-phase MRI, whereas lipomas are suppressed on fat-saturated images but not on opposed-phase images. From a clinical point of view, a distinction between the two is not important. Larger tumors must be differentiated from liposarcomas.[25,28,29]

Lipomatous pseudohypertrophy is an extreme variant of pancreatic fat accumulation resulting in a uniformly or focally enlarged pancreas, the exocrine system is replaced by fat, and no association can be found with obesity. The histologic features show diffuse replacement of normal pancreatic parenchymal tissue with mature adipose tissue, and the pancreatic acini have a scattered distribution. The pancreatic ductal system is intact.[30]

IS INTRA-PANCREATIC FAT ACCUMULATION REALLY A PATHOLOGICAL FINDING?

In 2007, Mathur *et al.* published their data comparing pancreatic fat and cytokine content in 30 leptin-deficient obese female mice and 30 lean control mice fed with a 15% fat diet for 4 weeks. After total pancreatectomy after 12 weeks, the pancreas organs from obese mice were heavier with a higher intrapancreatic fat content (total fat, triglycerides, cholesterol, and free fatty acids). Triglycerides represented 11% of pancreatic fat in lean mice compared with 67% of pancreatic fat in obese mice. Most interestingly, intrapancreatic cytokines interleukin-1beta and tumor necrosis factor-alpha were significantly elevated in the obese compared to lean mice. Therefore, the authors concluded that obesity results in an inflammatory process called NAFPD.[31] Meanwhile, the body of evidence has substantially increased suggesting that pancreatic lipomatosis is not only associated with metabolic syndrome, but together with nonalcoholic fatty liver disease and visceral fat acts as a visceral component of the metabolic syndrome with not only diagnostic significance but also pathogenetic relevance. Recent meta-analyses have established not only the link between excess IPFD and metabolic syndrome but also the association with an increased risk of arterial hypertension, type 2 diabetes mellitus, NAFLD, and central obesity.[32,33] Interestingly, IPFD occurs earlier in the course of metabolic syndrome than NAFLD. A pancreas without NASP nearly excludes the presence of NAFLD.[34]

Chronic exposure of pancreatic β-cells to high glucose and free fatty acid concentrations results in increased intracellular triglyceride accumulation and β-cell dysfunction. IPFD may affect predominantly the islets of Langerhans, but alternatively and in addition also acinar cells and interlobular stroma with acinar-to-adipocyte

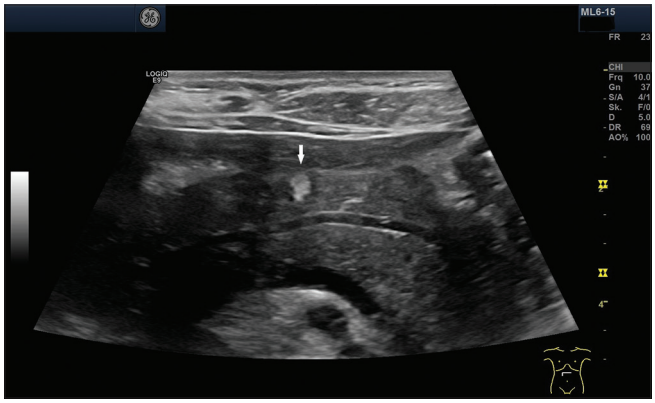

Figure 3. 39-year-old female. Non-Hodgkin's lymphoma in remission, very slim patient, BMI <20. In the pancreatic corpus a small hyperechoic lesion presents, which is not completely smooth bordered. In the course of 2 years, the lesion is unchanged. Differential diagnosis may be a small lipoma or a focal fat island. BMI: Body mass index

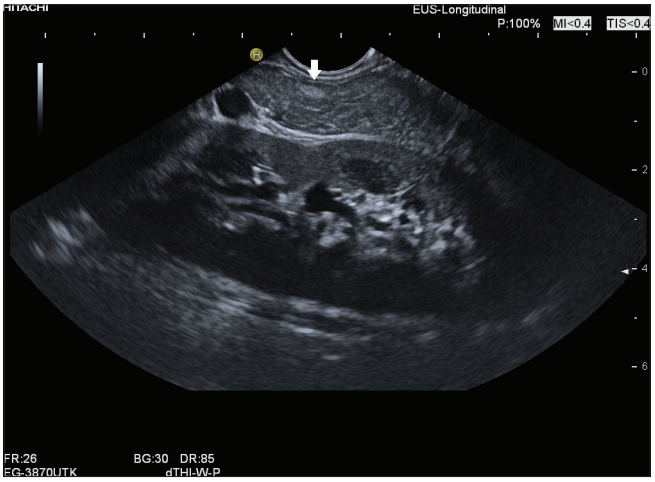

Figure 4. 40-year-old female. EUS to exclude choledocholithiasis. Incidental finding of a tiny hyperechoic lesion on the tail of the pancreas. On MRI, it appeared as a lipid island. On follow-up, the lesion was unchanged. MRI: Magnetic resonance imaging

transdifferentiation or adipocyte replacement of apoptotic acinar cells. Metabolic and morphologic consequences include decreased insulin secretion, insulin resistance, apoptosis of pancreatic exocrine cells, and replacement by adipocytes and connective tissue. This results in a positive feedback process or vicious cycle which, as part of the metabolic syndrome, can lead to various other clinical consequences in addition to the acceleration of type 2 diabetes mellitus and obesity. The associated clinical consequences include a tendency for acute pancreatitis to become more severe, the development of exocrine insufficiency, and also an increase in the risk of developing ductal adenocarcinoma with a potentially less favorable prognosis[23,35-38] [Table 2]. In an ultrasonographic study, pancreatic hyperechogenicity was shown to predict advanced fibrosis in NAFLD patients (odds ratio [OR] 10.52). On the other hand, the lack of pancreatic hyperechogenicity nearly excluded the presence of severe liver fibrosis.[62] Recently also correlations with subclinical atherosclerosis, epicardial fat, and increased intima–media thickness have been described.[37,63,64]

Due to the global obesity pandemic, NAFPD is observed increasingly with recent data reporting a prevalence of 33% (95% confidence interval 24%–41%) in a recent meta-analysis;[33] consequently, NAPFD is becoming a "hot topic" in both gastroenterology and endocrinology/diabetology.[35,38,65] Petrov and Taylor recently pointed out that FPD is more common than the two most common diseases of the endocrine pancreas (diabetes mellitus) and the exocrine pancreas (acute pancreatitis) combined.[35]

Interestingly, preliminary data suggest that IPFD and some of its clinical sequelae are in principle reversible processes.[66-70] As a consequence, pancreatic lipomatosis is a clinically relevant often incidental finding of abdominal imaging and must not longer be ignored or underreported. This is increasingly acknowledged, and

Table 2. Clinical relevance of excess intrapancreatic fat deposition

Clinical	Association
PDAC	The number of PanIN lesions in pancreatic surgery specimens is associated with intralobular fibrosis (OR: 5.61; 95% CI: 1.18-42.99) and intralobular pancreatic fat (OR: 17.86; 95% CI: 4.94-88.1) (Rebours *et al.*, 2015)[39]
	In patients operated for PDAC, the degree of pancreatic fatty infiltration was significantly higher compared to patients with pancreatduodenectomy performed for other cancers than PDAC (Hori *et al.*, 2014)[40]
	CT imaging: Pancreas-to spleen HU ratio<0.7 and decreased mean pancreatic HU are associated with the risk to subsequently develop PDAC
	Meta-analysis: Increased intra-pancreatic fat deposition is a significant risk factor for the development of PDAC or its precursor lesions (relative risk: 2.78, 95% CI: 1.56-4.94). (Fukuda *et al.*, 2017[41]; Hoogenboom *et al.*, 2021[42]; Janssens *et al.*, 2021[43]; Desai *et al.*, 2020[44]; Sreedhar *et al.*, 2020[45])
	EUS imaging: In patients who underwent EUS for hepatobiliary indications, fatty pancreas was significantly associated with pancreatic cancer (OR: 2.35, 95% CI: 1.04-5.33). (Khoury and Sbeit 2022)[46]
	In patients examined with EUS, fatty pancreas was the only significant risk factor for a diagnosis of PDAC fatty pancreas is the only significant risk factor for pancreatic cancer (OR: 18.027; 95% CI: 7.288-44.588). (Lesmana *et al.*, 2018)[47]
	In patients with IPMN, the diagnosis of concomitant pancreatic cancers was significantly associated with the presence of a hyperechoic pancreas (OR: 7.07, 95% CI: 1.48-33.80). (Mandai *et al.*, 2019)[48]
	Outcome: In patients operated for PDAC, the detection of metastatic lymph nodes was associated with the number of pancreatic adipocytes and mean survival was reduced in node-positive patients. (Mathur *et al.*, 2009)[49]
AP	Increased IPFD may predispose to the development of AP (1% increase of IPFD results in >30% risk of 1st attack of AP). (Ko *et al.*, 2022)[50]
	Fatty pancreas is significantly associated with a history of AP. (Sbeit and Khoury 2021)[51]
	IPFD is associated with the severity of AP. (Navina *et al.*, 2011[52]; Durgampudi *et al.*, 2014[53]; Xie *et al.*, 2019[54])
Exocrine pancreatic insufficiency	Pancreatic fat content is inversely correlated to pancreatic exocrine function (fecal elastase levels). (Kromrey *et al.*, 2019[55]; Krill *et al.*, 2022[56])
CP	In patients with CP, an elevation of circulating levels of periostin is observed which is associated with intra-pancreatic fat deposition. (Ko *et al.*, 2020)[57]
Postoperative pancreatic fistula	In a meta-analysis, fatty pancreas was a significant risk factor for the occurrence of postoperative pancreatic fistula. (Zhou *et al.*, 2021)[58]
Type 2 diabetes mellitus	Fatty pancreas is an independent significant risk factor for the subsequent development of type 2 diabetes, in particular in lean individuals. (Chan *et al.*, 2022[59]; Yamazaki *et al.*, 2020[60]; Hung *et al.*, 2018[61])

PDAC: Pancreatic ductal adenocarcinoma; AP: Acute pancreatitis; CP: Chronic pancreatitis; HU: Hounsfield units; PanIN: Pancreatic intraepithelial neoplasia; OR: Odds ratio; CI: Confidence interval; CT: Computed tomography; IPMN: Intraductal papillary mucinous neoplasm; IPFD: Intrapancreatic fat deposition

recent studies suggested to include the finding of IPFD in reporting of abdominal imaging procedures.[24,35,71]

ASSESSMENT OF PANCREATIC PARENCHYMAL FATTY INFILTRATION ON IMAGING

The parenchymal changes can be visualized in various imaging techniques. On ultrasound, the fatty induration of the pancreas appears hyperechoic. This is different from lipomas, which are hypoechoic. The cause of the hyperechogenicity on ultrasonography is not the fat but the changes in the architecture. Adipocytes develop within the interlobular septa. The hyperechogenicity is due to the alternation between glandular and fatty interfaces.[72,73]

In abdominal sonography, the echogenicity of the pancreas can be compared with the liver,[74-77] and that of the pancreatic tail with the spleen and left kidney.[34,77] However, the comparison with the liver is very subjective. This is especially true for obese patients or those with metabolic syndrome when steatosis hepatitis can be assumed. The tail of the pancreas cannot always be assessed on ultrasonography.[78,79] In obese patients with a thick obese abdominal wall, ultrasonographic visibility of the pancreas may be limited. High-grade lipomatosis of the pancreas can lead to dorsal sound attenuation. On the other hand, obese fat is also easily compressible with the transducer.

A first graduation of pancreatic echogenicity was done by Marks *et al.*,[74] which was also used in later studies:[75,80] (a) pancreatic echogenicity equal to hepatic echogenicity; (b) pancreatic echogenicity slightly greater than hepatic; (c) pancreatic echogenicity greater than hepatic; (d) the region of the pancreas is well seen but the echogenicity of the pancreas is sufficiently great so that the limits of pancreatic tissues (*vs.* boundary of retroperitoneal fat) could not be determined[74] [Table 3 and Figure 5].

On endosonography, the echogenicity of the pancreas can be compared with that of the spleen and left kidney, as the tail of the pancreas can always be seen here. Sepe *et al.*[81] compared the echogenicity of the pancreas with the spleen in endosonography. In addition, they assessed the parenchymal structure with delineation of the parenchymal "salt and pepper" there and the accessibility of the contours of the pancreatic duct.[81]

Grade I: 80% of the pancreatic parenchyma is hypoechoic or isoechoic compared to the spleen, the main pancreatic duct is clearly demarcated, and fine "salt-and-pepper spots" in the pancreatic parenchyma are clearly visible.

Grade II: >80% of the parenchyma is hyperechoic compared to the spleen, but the main pancreatic duct is delineable, and fine salt-and-pepper dots in the pancreatic parenchyma are clearly visible.

Grade III: >80% of the parenchyma are moderately more hyperechoic compared to the spleen, the margins of the main pancreatic duct are moderately obscured, and fine salt-and-pepper dots are moderately blurred.

Grade IV: 80% of the parenchyma is severely hyperechoic compared to the spleen, the pancreatic parenchyma cannot be demarcated from the adjacent retroperitoneal adipose tissue, the pancreatic duct is severely obscured, and fine, salt-and-pepper dots in the pancreatic parenchyma are strongly obscured.[81]

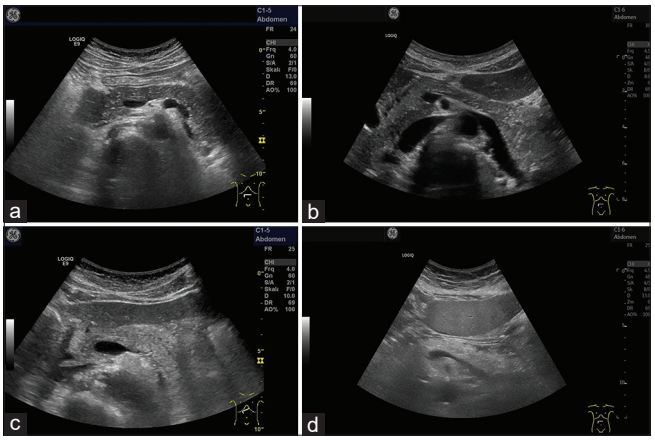

Figure 5. Graduation of pancreatic echogenicity in comparison to healthy liver on ultrasound according to Marks *et al*. and Worthen *et al*.: equal (a), slightly greater (b), greater than liver (c), and the region of the pancreas is sufficiently echogenic so that the boundary between pancreatic tissue and retroperitoneal fat could not be determined (d)

Table 3. Graduation of pancreatic echogenicity in comparison to healthy liver on ultrasound according to Marks *et al*. and Worthen and Beabeau[74,75]

Grade	Echogenicity of the pancreas parenchyma in relation to the normal liver
A	Equal
B	Slightly greater
C	Greater than liver
D	The region of the pancreas is sufficiently echogenic so that the boundary between pancreatic tissue and retroperitoneal fat could not be determined

Sepe *et al.*[81] evaluated grade I and II as normal pancreas and grade III and IV as fatty pancreas[81] [Table 4].

On CT adipose tissue shows a negative (-150 to -30 HU) attenuation without contrast medium. The attenuation of the pancreas is expected to decrease with fat infiltration. For glands showing diffuse attenuation, the mean attenuation of the regions of interest in different areas of the gland is used. The difference between pancreatic and splenic attenuation on CT is also used to quantify intrapancreatic fatty changes.[82]

MRI provides better soft-tissue resolution compared to CT and allows intrapancreatic fat to be detected without relying exclusively on attenuation. Different resonance frequencies are used to distinguish between fat and water protons. Thus, MR imaging allows sensitive assessment of tissue fat content.[82]

MR approaches to fat quantification of the pancreas include MR spectroscopy and imaging methods with early efforts focusing on chemical shift imaging (CSI) and evolving into spectral-spatial fat-selective, multipoint Dixon, and ultimately proton density fat fraction techniques.[83]

AGE-RELATED CHANGES OF PANCREATIC PARENCHYMA ECHOGENICITY ON ABDOMINAL ULTRASONOGRAPHY

Worthen and Beabeau[75] compared the echogenicity of the pancreas with the liver and found that both age and body wall thickness are determinants of increasing echogenicity and that they function independently.[75] This differentiation is important, as otherwise, it could be assumed that older people may have more abdominal fat and that the echogenicity of the pancreas as an expression of fat infiltration is not due to the age factor but to obesity and concomitant diseases.[75]

Glaser and Stienecker[76] compared the pancreas with the liver. Overweight patients were excluded so that the factors of obesity, high BMI, and abdominal fat could not be correlated a priori. The patients had no history of pancreatitis, no alcohol abuse, and no abnormal laboratory values regarding the hepatobiliary system and the pancreas. The pancreas echogenicity was categorized into four groups: lower, similar, higher, or distinctly higher compared to the liver.[76] They found an increasing pancreatic echogenicity with advancing age [Figure 6]. While the majority of those under 30 years of age had a pancreatic echogenicity similar to the liver, just as many of those aged 30–39 had higher echogenicity. This process continued with increasing age. In the over 40s, none had a lower pancreatic echogenicity than the liver and only a few had the same echogenicity as the liver. From the age >50 years, most patients showed a pancreatic echogenicity distinctly higher than that found in the liver. All patients over 80 years had distinctly higher pancreatic echogenicity compared to the liver. The difference of echogenicity was statistically significant between all age groups, except the group 50–59 and 60–69 years. The authors concluded that higher echogenicity at higher ages is a normal finding.[76]

Okada *et al.*[24] calculated a "brightness score" for the echogenicity of the pancreas during the ultrasound examination. The echogenicity of the pancreas was calculated as the number of pixels in 3 or 4 consistent areas in each pancreas. Three different brightness

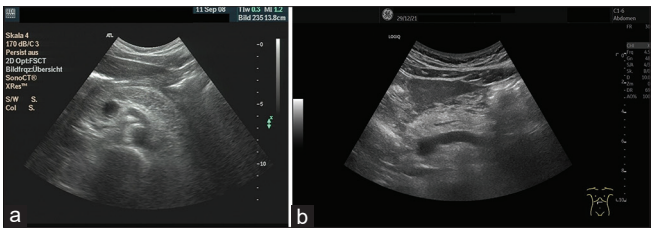

Figure 6. 61-year-old male. Nonspecific upper abdominal discomfort. Normal BMI, arterial hypertension, regular exercise. Pancreas at age 48 years old (a) and 61 years old (b). The pancreas is significantly more hyperechogenic at the older age of 61 years than at 48 years. BMI: Body mass index

Table 4. Endosonographic grading of pancreatic parenchymal fatty infiltration in comparison to the spleen according to Sepe *et al.*[81]

Grade	Echogenicity of the pancreas parenchyma in relation to the spleen	Parenchymal "salt and pepper" dots	Pancreatic duct
I	Isoechoic/or hypoechoic	Clearly visible	Delineable
II	Hyperechoic	Clearly visible	Delineable
III	Moderately hyperechoic	Moderately blurred	Margins moderately obscured
IV	Severely hyperechoic	Strongly obscured	Severely obscured

dimensions were divided.[24] Participants with fatty pancreas were older than those with normal pancreas: 61.8 ± 11.7 years versus 57.4 ± 14.0 years, respectively. Furthermore, participants with fatty pancreas had higher BMI, waist circumference, and prevalence of lifestyle-related diseases (arterial hypertension, diabetes mellitus type 2, dyslipoproteinemia, metabolic syndrome, and gallbladder stones) than those with a normal pancreas. Both male and female participants in the high brightness group were older and had higher BMI, waist circumference, and prevalence of lifestyle-related diseases. However, high waist circumference and age were shown to independently affect the pancreatic brightness score.[24]

Chantarojanasiri *et al.*[77] compared the pancreas with the liver, kidney, or spleen. A distinction was made between normal echogenicity and hyperechoic pancreas. The prevalence of hyperechoic pancreas echogenicity was 35% in the <40 years age group and increased to 63.6% in the >80 years age group. In addition, there were significant correlations between the presence of hyperechoic pancreas and BMI.[77]

UNEVEN FATTY INFILTRATION

Päivänsalo[84] examined the structure and size of the pancreatic parenchyma in patients without pancreatic disease using abdominal ultrasonography and CT. About half of the pancreatic organs were weakly echogenic and the other half were strongly echogenic. CT showed that 80% of the weakly echogenic pancreatic organs had a homogeneous structure and 20% were inhomogeneous and fatty. Of the highly echogenic pancreas, 25% were homogeneous and 75% were nonhomogeneous. The inhomogeneity of the echogenic pancreatic parenchyma suggests that fat infiltration may be unevenly developed. This inhomogeneity was even more rare in the low echogenic pancreas parenchyma and pronounced in most patients with the high echogenic pancreas. One could conclude from this that parenchymal fatty degeneration begins unevenly in spots. Fatty degeneration of the pancreas can affect the entire organ diffusely or present unevenly[84] [Figures 7 and 8].

Kawamoto *et al.*[85] describe that when fatty infiltration involves the pancreas diffusely, it is seen on CT as a separation of the parenchymal tissue by intermixed fat diffusely involving the entire pancreas. The individual lobules of the pancreatic parenchyma become more apparent separated by hypoattenuating fat. In more pronounced examples, fat becomes the predominant tissue of the pancreas.[85] This means that the lobules are initially left out and the fat infiltration is not uniformly diffuse.

An uneven fatty degeneration can occur in any area of the pancreas. The embryological ventral part of the head of the pancreas and the uncinate process are mostly left without focal fatty degeneration [Figure 9]. Most rarely, fatty degeneration is seen around the bile duct within the head of the pancreas.[72,73]

Atri *et al.*[86] showed in an autopsy study that the hypoechogenic embryological ventral part of the pancreatic head contained less fat than the embryological dorsal aspect. The histopathological lower fat infiltration in the embryological ventral part correlated with the lower echogenicity in ultrasound and hypoattenuation in CT. There was a significant increase in the difference of the attenuation of two aspects of the head of the pancreas with aging. The authors concluded that the hypoechoic embryological ventral aspect of the head of the pancreas seen on ultrasound examination is a normal variant.[86]

Dhillon *et al.* reported that the ventral pancreas can be differentiated from the dorsal pancreas by its absence or relatively scantiness of the number of intraparenchymal fat cells. In addition, Dhillon *et al.* concluded that the ventral pancreas had smaller, densely packed acini, smaller exocrine cells with smaller nuclei, scanty or absent interacinar fat, and more interlobular fibrous tissue than the dorsal pancreas.[87]

According to Matsumoto,[87] uneven fat induration is divided into a total of two types with two subtypes. In type 1, the posterior aspect of the head of the

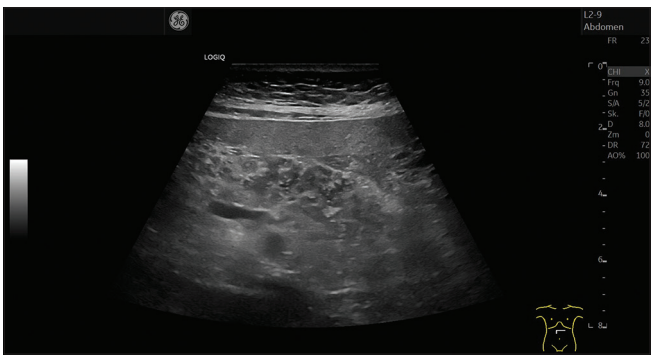

Figure 7. 70-year-old, male. Pneumonia. The pancreas shows mosaic-like fatty infiltration. In addition, honeycomb-like scarring changes present. The pancreatic duct is not dilated. There are no abdominal complaints, and pancreatitis has never occurred

pancreas was spared from intense fatty replacement. In type 2, the focal area around the common bile duct (CBD) was spared from fatty replacement. Each type was divided into two subgroups based on whether the body and tail of the pancreas showed intense fatty replacement (type a = negative for intense fatty replacement and type b = positive for intense fatty replacement). In type 1a (35% of cases), fatty infiltration is present only in the anterior parts of the pancreatic head. In type 1b (36% of cases), the anterior parts of the pancreatic head and the pancreatic body and tail show fatty infiltration. In type 2a (11% of cases), the entire pancreatic head is fattier except for the region around the CBD. In type 2b (18% of cases), the entire pancreas is fatty infiltrated except for the region around the CBD[72,87] [Figure 10].

Uneven fat infiltration was most prevalent in the 6th and 7th decades of life. The mean age of patients was 61 years for type 1a, 59 years for type 1b, 60 years for type 2a, and 66 years for type 2b. There were no statistically significant age differences between the individual types. The most pronounced fat infiltration is seen in types 1b and 2b, as the pancreatic body and tail are also included here. Type 2b had the highest average age[87] [Figure 10].

The embryological ventral pancreas-posterior part of pancreatic head and processus uncinatus-is then hypoechoic due to a lower fat involution. The clinical prevalence and morphological features of this normal variant were studied prospectively in a large series of 446 patients by Coulier.[73] The study confirmed the proportional increase in pancreatic echogenicity with age. In addition, 43% of women and 27% of men showed a hypoechoic embryological ventral apposition of the pancreatic head in higher age. This variant was not seen in any patient under 25 years of age and was most common in middle-aged women with a moderately hyperechoic pancreas.[73] Knowledge of nonfat indurated pancreatic parts is important in the differentiation of solid pancreatic tumors.

Koç and Taydaş[88] studied fat distribution in different pancreatic regions. Pancreatic steatosis was identified in a single anatomical region in 8.4%, two anatomical regions in 5.9%, and three anatomical regions in 18.4% of men. In women, steatosis was found in a single anatomical region in 10.4%, two anatomical regions in 5.4%, and three anatomical regions in 14.8%. The proportion of pancreatic steatosis

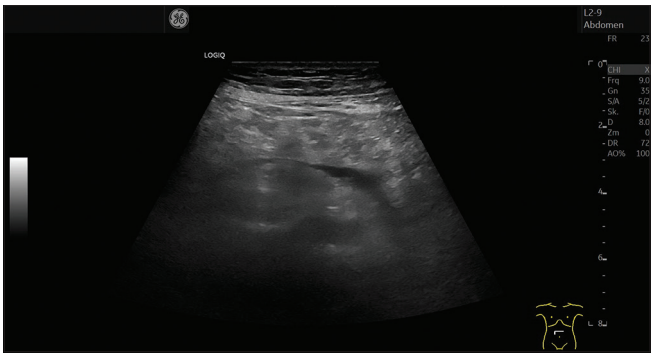

Figure 8. 72-year-old female. Arterial hypertension. Adjacent hyperechoic and non-hyperechoic areas are present in the pancreas. The pancreas shows diffuse nonuniform focal fatty infiltration

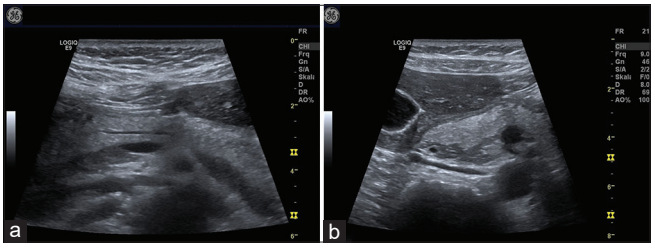

Figure 9. 56-year-old female. Hypoechoic ventral part of the pancreatic head – in ultrasound cross-section (a) and longitudinal section (b)

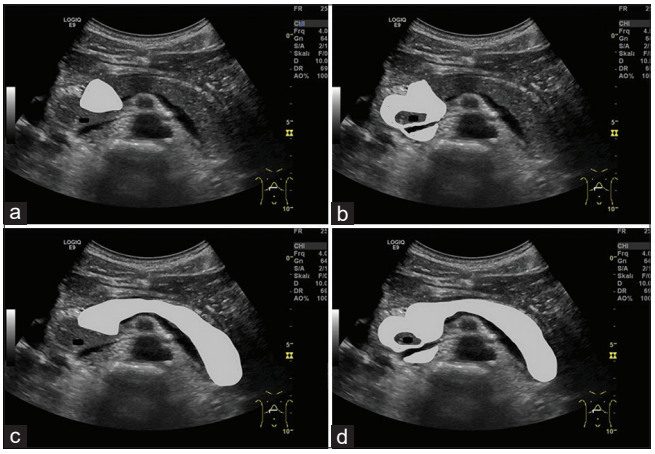

Figure 10. Focal fatty infiltration in the classification according to Matsumoto. Fatty infiltration is shaded: Type 1A (a); 2A (b); 1B (c); and 2B (d)

was 20% in the head-and-neck region, 26% in the pancreatic corpus, and 30% in the pancreatic tail for males and 18%, 23%, and 25%, respectively, for females. There was no significant difference between the sexes.[88] Koç and Taydaş[88] found a positive correlation between age and pancreatic steatosis and a positive correlation of age with anthropometric measures of the pancreas, atrophy of the pancreas, and calcification of the aorta and great vessels in their CT study. The regression analysis in their study showed that age is an independent risk factor that increases the risk of pancreatic steatosis.[88]

AGE-RELATED CHANGES OF PANCREATIC PARENCHYMA ON ENDOSONOGRAPHY

Rajan *et al.*[89] assessed parenchymal and duct changes in patients without diseases of the pancreas and hepatobiliary system and their age dependence in endosonography.[89] The frequency of EUS abnormalities in patients without clinical evidence of chronic pancreatitis increases with age, particularly after 60 years of age. The most common abnormality was hyperechoic stranding, followed by the accentuation of lobular pattern, irregular duct contour, echogenic foci, hyperechoic duct wall, cyst (s), and side-branch dilatation. Ductal narrowing, ductal dilatation, and calculi were not seen in any patient. At least one parenchymal and/or ductular abnormality was identified in 28% of the patients, with a trend of increasing abnormality with age: <40 years (23%), 40–60 years (25%), and >60 years (39%). Abnormalities in men were significantly higher compared with women, with 38% of men and 18% of women having an abnormality. Smoking, low alcohol consumption, BMI, and endoscopic findings were not significantly associated with abnormal EUS.[89] Elderly patients exhibited individual parenchymal criteria that are also included in the diagnosis of chronic pancreatitis. However, none had more than three criteria. In the diagnosis of chronic pancreatitis, features such as hyperechoic stranding or lobules, which were seen in this study, may be less specific than calcifications or narrowing of ducts.

In the EUS study of Petrone *et al.*,[90] the unique EUS finding significantly associated with age only was the dilation of the main pancreatic duct. Hyperechogenic foci of the parenchyma were correlated with both alcohol consumption and smoking, but not with age.[90]

Choi *et al.*[91] investigated associated factors for hyperechogenic pancreas on endosonography. On univariate analysis, age older than 60 years, obesity (BMI >25 kg/m^2), fatty liver, diabetes mellitus, hypertension, and hypercholesterolemia were identified as risk factors associated with hyperechogenic pancreas. On multivariate analysis, fatty liver, male gender, age older than 60 years, and hypertension were significantly associated with hyperechogenic pancreas. In the subgroup analysis, visceral adipose tissue was a statistically significant risk factor for hyperechogenic pancreas.[91]

ELASTOGRAPHY

Janssen and Papavassiliou[92] studied the stiffness of the pancreas using semi-quantitative EUS elastography. They found that the average strain values of the pancreas in the young- and middle-aged group (*i.e.*, age ≤60 years) and in the elderly group (age >60 years) are inversely proportional to the stiffness of the pancreas, suggesting that the pancreas is stiffer in the elderly. Semiquantitative elastography demonstrated that pancreatic organs become significantly harder during aging but remain softer than in chronic pancreatitis.[92]

Consistent data were also collected in a study with MR elastography.[93] The pancreatic stiffness significantly increased with age. The older age group (>45 years) had significantly higher stiffness compared to the younger group (≤45 years). No significant difference in stiffness measurements was observed between different anatomical regions of the pancreas, except neck stiffness was slightly lower compared to head and overall pancreas in healthy volunteers. The increase in stiffness is evidence of increasing fibrosis.[93]

Chantarojanasiri *et al.*[77] conducted a study on age-related changes in ultrasound-guided strain elastography of the pancreas, and the results were subjected to quantitative strain histogram analysis.[77] The authors had the hypothesis that the aging pancreas should become harder due to increased fibrosis. The hyperechoic pancreas that results from lipomatosis or fat deposition should result in a soft pancreas. The correlations between age and four elastographic parameters (mean, standard deviation, skewness, and kurtosis) and other findings, including hyperechoic pancreas, were investigated. Mean is the mean of the gray level: With higher values indicating softer tissue. Kurtosis corresponds to the peak of the gray level distribution with higher values indicating a concentration of specific hardness. The Skewness equals the asymmetry of the histogram, with higher values indicating larger or lower hardness. There was a significant correlation between increasing age and elastographic parameters such as the mean, skewness, and kurtosis, and these differences became significant after the age of 40. Means were lower in those with hyperechoic pancreas and a higher BMI. The prevalence of pancreatic hyperechogenicity increased, and the pancreatic hyperechogenicity was significantly negatively correlated with the mean.[77] The results suggest a higher stiffness of the hyperechoic pancreas of the elderly.

AGE-RELATED CHANGES OF PANCREATIC PARENCHYMA ON COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

The external contour of the pancreas shows an age-related development. The smooth-bordered contour becomes rarer. Pancreatic lobulation increases not only in frequency with age but also in degree, and with advanced age a lobular outer contour is common.[94] While in the 3rd decade, almost exclusively a homogeneous structure is found, in the 4th decade, one-third of the pancreases show a patchy structure. This structure becomes more frequent with age and is 71% of the cases in the 8th decade of life.[94] This is possibly due to multifocal intralobular fibrosis with aging. With age, the AP diameter of the pancreatic head, body, and tail decreases.[94] In CT, Heuck *et al.*[94] measured an average diameter of 28.6 (±3.8) mm in the area of the pancreatic head in 20–30 years olds. This decreased to 24.0 (±3.6) mm in the 6th decade of life and to 21.2 (±4.3) mm in 70–80 years olds.[94] However, apart from the predominant atrophic pancreas, there were also some cases with less pronounced involution.

Sartoris *et al.*[95] found in a CT study that the pancreas surface lobularity was correlated with age and BMI. Patients with pancreatic diseases and diabetes mellitus were excluded. Challenging the interpretation, age was again correlated with a higher BMI in this study.[95] Therefore, it is critical to see whether the contour changes are really a process that occurs because of age-related morphological changes or whether older people tend to have a higher BMI and are sicker. The MRI study by Sato *et al.*[96] is clearer in this respect. Patients with severe obesity were excluded. The pancreatic AP diameter was significantly reduced, and lobulation and parenchymal fatty change became more evident with aging.[96] The strongest correlation was found between aging and the pancreatic tail AP diameter. MRI analysis showed that the pancreatic AP diameter significantly reduced with age and pancreatic atrophy progressed, most likely due to the progress of fibrosis. Pancreatic fatty infiltration significantly progressed with aging. The authors concluded that the progression of pancreatic lobulation is likely to be associated with pancreatic fibrosis, fatty infiltration, and a reduction in pancreatic acinar cells.[96]

PANCREATIC VOLUME AND FAT VOLUME

Saisho *et al.*[9] studied pancreatic parenchymal volume and fat volume during aging. The pancreas volume increases in a linear fashion from birth to age 20 years. It changes little between the ages of 20 and 60 years. The parenchymal pancreas volume reaches a maximum in both men and women in the third decade of life and remains constant until the age of 60. After that, the parenchymal volume gradually decreases in both sexes.[9] Saisho *et al.*[9] showed in their CT study that pancreatic fat volume increases with age. In men, pancreatic fat volume increases in the third and fourth decades of life and then remains constant until the seventh decade of life. In contrast, pancreatic fat volume in women was remarkably unchanged during the second to the ninth decade of life. In adults past 60 years of age, both total and parenchymal pancreas volumes gradually decline. The accumulation of fat in the pancreas was increased in obese *versus* lean subjects. The fat-to-parenchyma ratio increases in that age group.[9] One can speculate that older patients have pancreatic lipomatosis due to diabetes mellitus type 2. However, the authors demonstrated that there was no increase in pancreatic fat in type 2 diabetes whether measured by a CT imaging-based approach or by histology at autopsy.[9] This is consistent with the findings of the SHIP study that the fat content of the pancreas on MRI is related to older age and higher BMI, but not related to prediabetes or diabetes.[8]

In 2019, Wang *et al.*[97] reported that the tail of the pancreatic gland on MRI in the 50–59 age group and all segments of the pancreatic gland at ages 60–69, 70–79, and 80–89 were significantly more atrophic compared to the 20–29 age group[97] [Figure 11].

GENDER

Healthy women had a higher pancreatic fat fraction than their male counterparts of the same age.[98] Using chemical shift imaging (CSI), Yang *et al.*[99] found that pancreatic fat percentage remained unchanged in healthy women with normal BMI between 20 and 40 years of age but increased significantly by 70.0% and 25.9% between 41 and 50 years of age and 51 and 70 years of age, respectively. These results suggest that the increase in pancreatic fat begins in the fifth decade of life. The pancreatic fat fraction of postmenopausal women was significantly higher than that of premenopausal women of the same age (46–49 years), respectively.

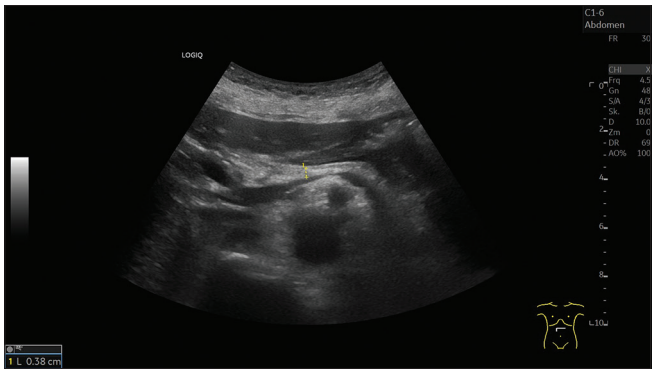

Figure 11. 90-year-old female. Nonspecific abdominal complaints, very slim patient, diabetes mellitus type 2, requiring tablets. Ultrasonography shows high-grade atrophy of the pancreas with hyperechoic parenchyma

The pancreatic fat fraction of healthy women aged 41–70 years was still higher than that of women aged 20–40 years, which suggested that aging was an independent risk factor for pancreatic fat deposition in healthy women and that both aging and menopause were responsible for the increased pancreatic fat fraction of healthy women older than 40 years. While in healthy men the increase in the fat fraction in the pancreas began in the 6th decade of life, in healthy women, fat infiltration in the pancreas occurred about 10 years earlier than in healthy men. The authors suspected that additional factors to aging had an influence. It is discussed that estradiol and progesterone protect the pancreas from lipomatosis, by stimulating pancreatic cell proliferation, reducing pancreatic oxidative stress, and attenuating acinar cell apoptosis.[99,100] The decline in estradiol and progesterone levels after menopause reduces their protective effect on the pancreas and can lead to fatty infiltration of the pancreas.[99] In abdominal ultrasonography, higher echogenicity of the pancreas in healthy, nonobese women can be explained by hormonal differences.

SUMMARY

With aging, fibrosis, fat deposition, and atrophy occur in the pancreas. Imaging shows that pancreatic parenchymal volume and AP diameter decrease and fat volume increases. Ultrasonographically, the pancreas is increasingly echogenic. In advanced age, the hyperechogenic pancreas is a common finding. This can be seen as a normal finding unless other major risk factors such as obesity and high BMI are present, which also correlate with fatty infiltration. Aging cannot be prevented, but lifestyle factors should be influenced. In healthy women, fat infiltration occurs earlier than in healthy men due to hormonal changes. Fat infiltration can be uneven. Focal reduced fatness of the embryological ventral part is a physiological finding and increases with age. Fibrosis and fatty infiltration of the pancreas may be associated with exocrine pancreatic insufficiency in the elderly. In case of dyspeptic complaints and weight loss, exocrine pancreatic insufficiency should always be considered and substituted as needed. In younger patients, a fatty pancreas on imaging is a finding with potential clinical relevance and should be included in imaging reports.

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Conflicts of interest

Siyu Sun is the Editor-in-Chief of the journal; Christoph F. Dietrich is a Co-Editor-in-Chief; Christian Jenssen, Michael Hocke and Julio Iglesias-Garcia are Editorial Board Members. This article was subject to the journal's standard procedures, with peer review handled independently of the editors and their research groups.

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