Metabolic implications of pancreatic fat accumulation

Robert Wagner[1,2,3,13], *Sabine S. Eckstein*[1,2,13], *Hajime Yamazaki*[4], *Felicia Gerst*[1,2,3], *Jürgen Machann*[1,2,5], *Benjamin Assad Jaghutriz*[1,2,3], *Annette Schürmann*[2,6,7], *Michele Solimena*[2,8,9], *Stephan Singer*[10], *Alfred Königsrainer*[11], *Andreas L. Birkenfeld*[1,2,3], *Hans-Ulrich Häring*[1,2,3], *Andreas Fritsche*[1,2,3], *Susanne Ullrich*[1,2,3] *and Martin Heni*[1,2,3,12]✉

Abstract | Fat accumulation outside subcutaneous adipose tissue often has unfavourable effects on systemic metabolism. In addition to non-alcoholic fatty liver disease, which has received considerable attention, pancreatic fat has become an important area of research throughout the past 10 years. While a number of diagnostic approaches are available to quantify pancreatic fat, multi-echo Dixon MRI is currently the most developed method. Initial studies have shown associations between pancreatic fat and the metabolic syndrome, impaired glucose metabolism and type 2 diabetes mellitus. Pancreatic fat is linked to reduced insulin secretion, at least under specific circumstances such as prediabetes, low BMI and increased genetic risk of type 2 diabetes mellitus. This Review summarizes the possible causes and metabolic consequences of pancreatic fat accumulation. In addition, potential therapeutic approaches for addressing pancreatic fat accumulation are discussed.

Currently, no widely accepted terminology for fat accumulation in the pancreas has been established. Various terms, such as 'pancreatic steatosis'[1,2], 'pancreatic lipomatosis'[3,4], 'fatty infiltration of the pancreas'[5,6], 'non-alcoholic fatty pancreas'[7] and 'pancreatic fat accumulation'[8,9], can be found to describe this phenomenon. A 2011 review proposed that pancreatic steatosis should refer to fat accumulation in the pancreas in general[10]. The irreversible infiltration of fat as a consequence of acinar cell death could be called pancreatic replacement, while the potentially reversible obesity-mediated accumulation of pancreatic fat could be termed fatty infiltration or non-alcoholic fatty pancreas disease[10]. Given that pancreatic replacement and non-alcoholic fatty pancreas are difficult to differentiate in practice, this Review uses the general term 'pancreatic steatosis' to refer to all cases of fat accumulation in the pancreas unless otherwise stated.

The prevalence of pancreatic steatosis in the general population is estimated to lie between 16% and 35%[11–14], depending on ethnicity and age. Fat storage in the pancreas might be the result of adipocyte infiltration or intracellular ectopic accumulation as lipid droplets. Adipocyte infiltration in the exocrine pancreas is the most common degenerative change in the pancreas found in multiple autopsy studies[3,15]. An extensive degree of fatty infiltration has been observed in 23–48% of all pancreatic histological sections and has been described as a phenomenon that diffusely affects the whole organ[3,16]. While intracellular ectopic lipid storage within islet cells increases during ageing and with development of type 2 diabetes mellitus (T2DM)[17,18], the majority of pancreatic lipids are stored in adipocytes that reside in the exocrine pancreas and, to a lesser extent, in the endocrine pancreas[19–21]. Pancreatic adipocytes express adiponectin and leptin and store triglycerides in a large lipid droplet (FIG. 1)[20,22]. Replacement of pancreatic exocrine tissue (which accounts for about 95–98% of the pancreas[19,23]) with adipose tissue was observed in cotton rats prone to metabolic disorders[24] as well as in albino rats as a result of pancreatic duct ligation, which left islets of isolated Langerhans cells surrounded by adipose tissue[15]. In addition, a case report of an autopsy in an older patient described almost complete replacement of acini with adipocytes and (presumably normal) islets embedded within the adipose tissue[25].

Detection of pancreatic fat

Histology

Histological examination of pancreas specimens enables the detection and localization of fat within the organ. However, due to its anatomical location, the pancreas is only accessible for tissue sampling via a direct surgical approach or endoscopy. Therefore, in the absence of a clear medical indication, tissue sampling of the pancreas is not practicable in daily hospital routine. Our current histological information about pancreatic fat accumulation is therefore based upon studies

✉*e-mail: martin.heni@med.uni-tuebingen.de*

https://doi.org/10.1038/s41574-021-00573-3

Key points

- A number of studies have demonstrated a link between pancreatic fat and impaired glucose metabolism, as well as between pancreatic fat and type 2 diabetes mellitus.
- Possible causes of pancreatic steatosis include the metabolic syndrome, non-alcoholic fatty liver disease, alcohol consumption and specific genetic diseases.
- Chronic accumulation of fat in the pancreas can lead to chronic pancreatitis, pancreatic neoplasia, disturbed glucose metabolism and impaired insulin secretion.
- Different approaches, such as a hypocaloric diet, exercise, bariatric surgery and pharmacological interventions, can reduce pancreatic fat content.
- Preliminary evidence shows that a reduction in pancreatic fat improves insulin metabolism, but further experimental evidence is needed to untangle the underlying mechanisms.

Echogenicity
The ability of a surface to reflect ultrasound in ultrasonography.

Attenuation
The radiological absorption of X-rays.

Hounsfield units
(HU). Units for quantitatively describing the radiodensity of different body tissues and materials, standardized in relation to the attenuation coefficients of air (−1,000 HU) and distilled water (0 HU), named after the developer of CT, Sir Godfrey Hounsfield.

that analysed samples taken during pancreatic surgery or autopsy[20,26]. One limitation of such a histological specimen collection is that the sample obtained might not necessarily be representative of the entire organ. Furthermore, the underlying disease that prompted surgery, such as cancer or chronic inflammation, might have an impact on pancreatic architecture and fat accumulation.

Imaging

The non-invasive detection and quantification of pancreatic fat accumulation by imaging techniques enables the assessment of fat accumulation in the entire pancreas. This visualization can be challenging for a number of reasons. The pancreas lies in the retroperitoneal space of the upper abdomen, has a typical length of 12–15 cm, a maximum width of about 5 cm and a thickness of approximately 2–3 cm. Due to its lobular form and location between the gastrointestinal tract and intra-abdominal adipose tissue, the pancreas cannot always be reliably differentiated from its surrounding structures. Furthermore, a standardized grading system for the assessment of pancreatic fat accumulation by imaging techniques has yet to be established. There is still a considerable amount of variation in the feasibility, availability, reproducibility and costs of existing imaging methods. These currently include ultrasonography[27], endoscopic ultrasonography[28], CT[27,29], proton magnetic resonance spectroscopy (^{1}H-MRS)[30] and MRI[31] (BOX 1).

Ultrasonography. Transabdominal ultrasonography is a non-invasive method for the visualization of pancreatic tissue and detection of fat accumulation within the organ. The advantages of this technique are that it is widely available, faster than many alternative imaging techniques and inexpensive. Pancreatic ultrasonography has therefore been applied in a number of large cohorts comprising up to 32,000 participants[27,32–34]. Pancreatic steatosis is usually diagnosed by comparing the echogenicity of the pancreas with that of the kidney or spleen[32,35]. As the kidney and pancreas often cannot be compared in the same imaging window, the pancreas to kidney contrast can be indirectly obtained by comparing the differences between hepatic and renal echogenicity and then between hepatic and pancreatic echogenicity[27,35]. Assessment of the pancreas using transabdominal ultrasonography has several major limitations. First, objective standards for quantification of ultrasonographic images have not been established. Second, the sensitivity and specificity of this method depend largely on the investigator and on patient characteristics. For example, patient obesity and the presence of intestinal air are the most frequent limitations in obtaining satisfactory ultrasonographic images[36,37]. In addition to conventional transabdominal ultrasonography, endoscopic ultrasonography has also been deployed to assess pancreatic fat content[14,28,38]. While it provides unobstructed visualization due to the shorter distances between the measurement device and area of interest[14,28], endoscopic ultrasonography shares other limitations of transabdominal ultrasonography such as operator dependency. Additionally, the requirement for an endoscopic examination makes the procedure more laborious than transabdominal ultrasonography. Overall, ultrasonography does not provide a precise and unbiased quantification of pancreatic fat. To the best of our knowledge, there are still no studies that have investigated the sensitivity and specificity of ultrasonography in comparison with histology.

Computed tomography. CT is another commonly applied method for the quantification of pancreatic fat. CT is less expensive than many other imaging techniques, readily available, and more sensitive and specific than ultrasonography[29,39]. As CT involves exposure to ionizing radiation, its application in clinical research is limited. When correlated with histological quantification, the difference between pancreatic and splenic attenuation on CT shows a moderate correlation coefficient of −0.62 (REF.[40]). In CT images, the radiodensity of different tissues and organic substances is quantified using Hounsfield units (HU). Adipose tissue has negative values of around −130 to −90 HU[20]. As the Hounsfield scale can show slight variations depending on acquisition and reconstruction parameters, pancreatic fat is compared with an internal reference tissue with no lipid content, such as the spleen[41,42]. Non-enhanced

Author addresses

[1]Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, Tübingen, Germany.
[2]German Center for Diabetes Research (DZD), Tübingen, Germany.
[3]Department of Internal Medicine, Division of Diabetology, Endocrinology, and Nephrology, Eberhard Karls University Tübingen, Tübingen, Germany.
[4]Section of Clinical Epidemiology, Department of Community Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan.
[5]Section of Experimental Radiology, Department of Diagnostic and Interventional Radiology, Eberhard Karls University Tübingen, Tübingen, Germany.
[6]Department of Experimental Diabetology, German Institute of Human Nutrition (DIfE), Potsdam-Rehbrücke, Germany.
[7]Institute of Nutritional Science, University of Potsdam, Potsdam, Germany.
[8]Molecular Diabetology, University Hospital and Faculty of Medicine Carl Gustav Carus, TU Dresden, Dresden, Germany.
[9]Paul Langerhans Institute Dresden (PLID), Helmholtz Center Munich, University Hospital and Faculty of Medicine Carl Gustav Carus, TU Dresden, Dresden, Germany.
[10]Institute of Pathology, University of Tübingen, Tübingen, Germany.
[11]Department of General, Visceral, and Transplant Surgery, University Hospital Tübingen, Tübingen, Germany.
[12]Institute for Clinical Chemistry and Pathobiochemistry, Department for Diagnostic Laboratory Medicine, University Hospital Tübingen, Tübingen, Germany.
[13]These authors contributed equally: Robert Wagner, Sabine S. Eckstein.

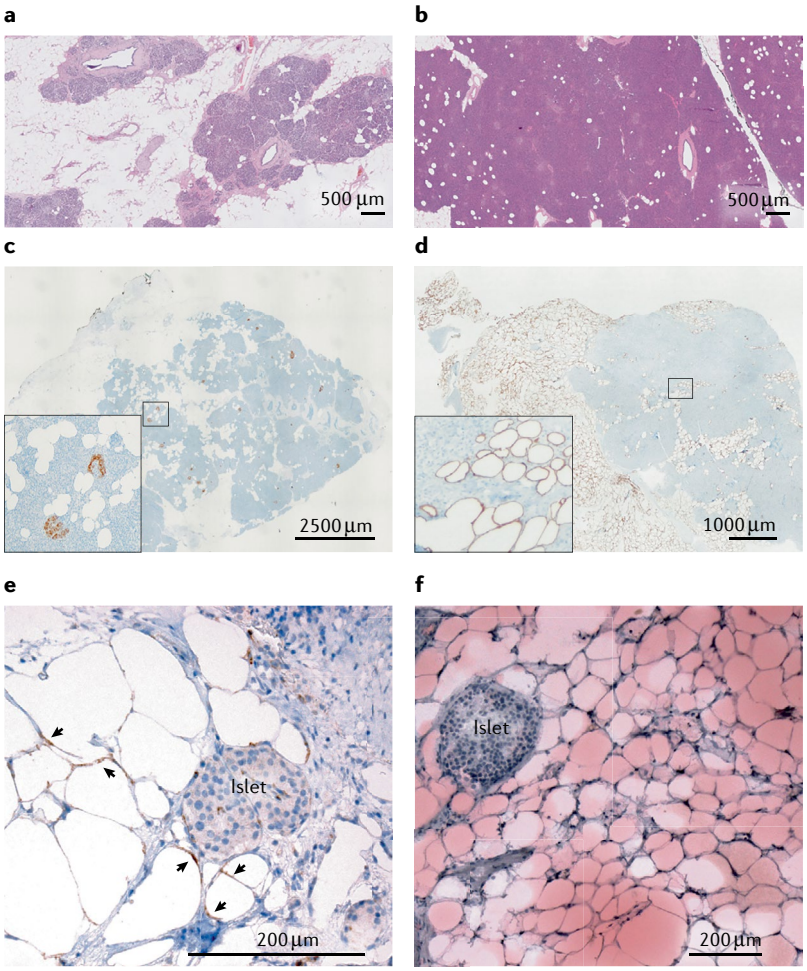

Fig. 1 | **Histological detection of fat accumulation in adipocytes in pancreatic tissue.** Marked pancreatic steatosis in non-tumorous tissue from a 76-years-old patient (part **a**). Low fat content in non-tumorous tissue from a 63-year-old patient (part **b**). Human pancreas sections stained for insulin (part **c**), leptin (part **d**), adiponectin (arrowheads) (part **e**) and triglycerides (part **f**) (Oil O red). Haematoxylin was used as counter-stain in all preparations.

Dixon method
An MR imaging technique that enables separation of fat and water by the inherent chemical shift difference of protons bound to lean tissues and lipids, named after the American physicist and developer W. Thomas Dixon.

Proton density fat fraction
The proton density fat fraction is a non-invasive and accurate measure of the percentage of fat infiltration in organs calculated from multi-echo Dixon images.

T2*
An effective transverse relaxation time resulting from the inherent transverse relaxation time T2 and microscopic magnetic field inhomogenities in MR gradient echo images.

CT images are required for the quantification of pancreatic fat[40], as radiocontrast agents cause changes in radiodensity.

^{1}H-MRS. A further technique for the assessment of pancreatic fat is ^{1}H-MRS[12,30]. Due to its high cost, limited availability and required high operator expertise, ^{1}H-MRS is not often used to measure pancreatic fat[43,44]. In addition, localized ^{1}H-MRS requires a large volume of interest (for example, 1 × 1 × 2 cm) that needs to be properly positioned in a defined region of the pancreas. As the measurement might be affected by breathing or coughing, there is no guarantee that the spectrum has been acquired exclusively from pancreatic tissue, as the surrounding tissue (such as extralobar adipose tissue) might enter the measurement field and confound the resulting fat fraction. Thus, the repeatability and reproducibility of pancreatic ^{1}H-MRS measurements are rather poor[45].

MRI. One commonly used method for the precise quantification of pancreatic fat accumulation is MRI[4,31,44]. By applying the Dixon method, images can be post-processed to yield water-selective or fat-selective images[46]. Advanced multi-echo Dixon techniques facilitate the calculation of the proton density fat fraction in tissues by correcting for the effective transverse relaxation rate T2*[47,48]. These techniques are available for most common field strengths (measured in tesla; that is, 1.5 T and 3 T[49,50]) and scanners from large device manufacturers such as GE Healthcare (IDEAL IQ[51]), Philips Healthcare (mDIXON[52]) and Siemens Healthineers (LiverLab qDixon[53]). Based on an inherent excellent linearity and reproducibility, these techniques enable reliable and reproducible mapping of pancreatic proton density fat fraction. FIGURE 2 provides an example of two individuals with low (FIG. 2a) and high (FIG. 2b) levels of pancreatic fat, as acquired using a six-point Dixon sequence on a 3 T whole-body imager. MRI has good specificity and sensitivity and is now widely used as a reliable method for the quantification of pancreatic fat[4,45,54,55]. It has also been shown to be correlated with histologically assessed fat content with a correlation coefficient of 0.71 (REF.[56]).

Nevertheless, just like the other radiographic techniques, MRI has limitations with regard to availability, high acquisition cost and the time-consuming nature of the examination procedure. MRI is also prone to observer-dependent bias as the distribution of fat in the pancreas can be utterly inhomogeneous with very bright local fat inclusions that superimpose on an almost homogeneous background (FIG. 1b). Thus, a small region of interest should be carefully chosen for determination of pancreatic fat content to avoid misinterpretation. Regional differences of fat accumulation between the pancreatic head, body and tail have been described[31,57]. These differences must be considered, for instance by calculating mean pancreatic fat content. To minimize partial volume bias (such as contamination by surrounding visceral adipose tissue), acquiring thin slices (between 3 mm and 6 mm) is recommended. Additionally, inclusion of non-parenchymal tissues, such as pancreatic ducts, and intrusions of visceral adipose tissue fat can be minimized by thresholding the images (so-called MR-opsy[44]), leading to improvement in the inter-observer coefficient of variation that is otherwise markedly higher for the pancreas than for the liver[58,59].

Is there short-term variability in pancreatic fat content? Up to now, little is known about the acute turnover rate of pancreatic fat; to the best of our knowledge there is currently no reference in the literature addressing the regulation of pancreatic fat content. It is well described that levels of intramyocellular lipids show strong diurnal changes in skeletal muscle[60] and that intrahepatic fat remains almost unchanged in the course of a short-term dietary intervention[61]. Our own preliminary data, currently available as a preprint[62], argue against major diurnal or dietary effects, but further studies are clearly needed to finally clarify this finding.

Causes of pancreatic fat accumulation

Associations between pancreatic fat accumulation and different medical conditions, as well as links with anthropometric or metabolic parameters, have been

Tesla
A unit of magnetic field strength. Typical clinical MR scanners work with field strengths between 1.5 T and 3 T.

Linearity
Describes the relationship between the measured signal and concentration/amount of the assessed substance, e.g. amount of lipids within the pancreas.

investigated[11,29–31]. The main factors affecting pancreatic fat accumulation are the metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), age and alcohol consumption; however, other factors, such as sex hormones, low birthweight and some monogenetic conditions, might also be involved.

The metabolic syndrome

According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP-III), the presence of several criteria confirms the diagnosis of the metabolic syndrome: abdominal obesity, hypertension, dyslipidaemia and insulin resistance or overt T2DM. Several studies have found an association between the metabolic syndrome and an increased prevalence of pancreatic steatosis. These studies were conducted in people from different ethnic backgrounds, including Asian and European ancestry[2,14,32,63,64]. Therefore, metabolic features that are more prevalent in people with certain ethnic backgrounds have been linked to pancreatic fat accumulation. These features include increased BMI and obesity[8,29,31,65,66]. By assessing the relationship between pancreatic fat and BMI, we have shown that pancreatic fat is positively associated with BMI independent of sex and age[31]. This finding is at least partly due to visceral obesity, as visceral adipose tissue is positively associated with pancreatic steatosis[27,31,67]. Further components of the metabolic syndrome, such as arterial hypertension and hyperlipidaemia, have also been reported to be associated with increased pancreatic fat content[14,68]. A longitudinal, 5-year follow-up study in people with prediabetes has further suggested that elevated BMI and prediabetes are predictive of the development of pancreatic steatosis[39].

Box 1 | Approaches for the quantification of pancreatic fat content

While all approaches can provide information on the absence or presence of pancreatic fat in general, their sensitivity and specificity are very different. Each technique has its own advantages and disadvantages, so the appropriate approach strongly depends on the setting.

Histology enables the detection of cellular and subcellular localization of fat storage. This approach is prone to selection bias (non-representative sampling). In addition, the approach is very invasive and might be influenced by the medical condition that prompted surgery.

Ultrasonography enables a semiquantitative assessment of pancreatic fat. In this approach, organ echogenicity is compared with that of the renal parenchyma or spleen. The approach is strongly investigator-dependent; visibility can be limited by air in the gastrointestinal tract or by excessive abdominal adiposity.

CT is more precise and reproducible than ultrasonography, is widely available, has short acquisition times and has high spatial resolution. A major limitation of CT is exposure to ionizing radiation. In addition, an internal reference for estimation of pancreatic fat content is advised (for example, the spleen).

Proton magnetic resonance spectroscopy (^{1}H-MRS) involves no exposure to ionizing radiation. However, this approach requires a large scanning volume (1–2 cm^3) that might be contaminated by extrapancreatic structures (e.g. fat outside the pancreas), poor repeatability and poor reproducibility. A long measurement time (approximately 1–2 min) is also required.

MRI (multi-echo Dixon imaging) is performed by quantitative evaluation of MRI-derived proton density fat fraction. The approach involves no exposure to ionizing radiation, has high reproducibility and good spatial resolution, and covers the entire organ. Regional differences in fat content and partial volume effects have to be considered. This approach has a short measurement time (15 s).

Non-alcoholic fatty liver disease

There is a clear link between NAFLD and obesity, the metabolic syndrome and T2DM. Multiple studies have found associations between liver fat content and pancreatic steatosis[8,58,69–72]. However, in many studies it was unclear whether this association was confounded by other variables, such as obesity or increased visceral adipose tissue content[58,70,72]. A nested case–control study ascertained that NAFLD was associated with increased pancreatic fat independent of sex, age, BMI and T2DM status[69]. In further studies, adjustment for visceral adipose tissue volume[8] or BMI[71] removed the association between NAFLD and pancreatic fat. Correlative data from the DIRECT trial suggest that hepatic lipid accumulation can be a major determinant of pancreatic steatosis[73]. According to this hypothesis, an increased export of hepatic triglycerides leads to pancreatic fat accumulation, which in turn affects adequate insulin secretion and results in increased glycaemia[74,75] Visceral and subcutaneous adipose tissue, that are major sources of circulating fatty acids, could also contribute to pancreatic steatosis[76]. The finding that increased pancreatic fat accumulation is observed in insulin resistance, a condition associated with increased circulating levels of non-esterified fatty acids, also point towards a probable connection.

A number of studies did not find connections between pancreatic steatosis and severity or activity of NAFLD[58,71,72]. In addition, in a longitudinal study, hepatic fat content was not predictive of future pancreatic fat accumulation[39]. These data could point to a liver-independent deposition of fatty acids in the pancreas, potentially as a direct flux from adipose tissue independent of hepatic fat export[76]. In view of the different study populations and methods of liver and pancreas fat assessments, further investigations are required to clarify the relationship between fat accumulation in the liver and pancreas and to identify potential confounders.

Age

Increasing age has consistently been associated with pancreatic fat accumulation[3,26,29]. Several autopsy studies with a total of more than 500 people found higher levels of pancreatic fat with increasing age[3,26]. A cross-sectional study found increasing pancreatic fat starting in childhood and reaching a plateau in middle-aged adults (FIG. 3). This change was accompanied by an increase in pancreatic parenchyma volume. Once participants reached 60 years of age, the volume of their pancreatic parenchyma decreased, resulting in a proportionately higher fat content in older than in younger individuals[29]. A shift from parenchyma to fat in the pancreas thus seems to be a physiological process during ageing.

Other potential contributors

Alcohol intake induces fat accumulation in the liver and is a well-known risk factor for pancreatitis[77,78]. Even moderate alcohol consumption (more than 14 g per week) is associated with increased pancreatic steatosis as assessed by endoscopic ultrasonography[28]. Men with obesity have been reported to have more fat in their pancreas than women with obesity[66], suggesting that sex hormones might influence the accumulation of

pancreatic fat. However, it is still unclear which sex hormones contribute and what the underlying mechanisms might be.

Furthermore, adults who had an extremely low birthweight are more prone to pancreatic steatosis than adults with a birthweight in the normal range[79]. Low birthweight has also been associated with an increased risk of T2DM, obesity and cardiovascular disease risk[80]. In addition, maturity onset diabetes of the young type 8, a monogenic type of diabetes caused by heterozygous mutations in the carboxyl ester lipase gene (*CEL*), is associated with severe pancreatic lipomatosis from early childhood[81]. In line with observations in humans[82], mouse studies have indicated that genetic background contributes to the susceptibility to accumulate adipocytes in the pancreas. The diabetes-prone New Zealand obese (NZO) mouse, which develops a similar phenotype to patients with T2DM and β-cell failure, exhibits a fatty pancreas (due to adipocyte accumulation in the pancreas) and a fatty liver (due to ectopic fat in hepatocytes)[83]. By contrast, C57BL/6-*ob*/*ob* mice, which are obese but resistant to diabetes mellitus, have a very low number of adipocytes in the pancreas and ectopically store fat primarily in the liver[83]. Although some genes associated with diabetes mellitus have already been discovered in NZO mice, it is not yet clear which of these genetic factors contribute to the accumulation of adipocytes in the pancreas[84]. Several monogenetic diseases, such as cystic fibrosis[85–88] and Shwachman–Diamond syndrome[89], are also linked to increased pancreatic fat content. In addition, other genetic diseases, such as β-thalassaemia[90–92] and Diamond–Blackfan anaemia or hereditary haemochromatosis[93], are also associated with pancreatic steatosis.

Chronic stenosis or occlusion of the pancreatic duct, often as a result of cancer, can also lead to exocrine tissue atrophy and its subsequent replacement by adipose tissue[15,94].

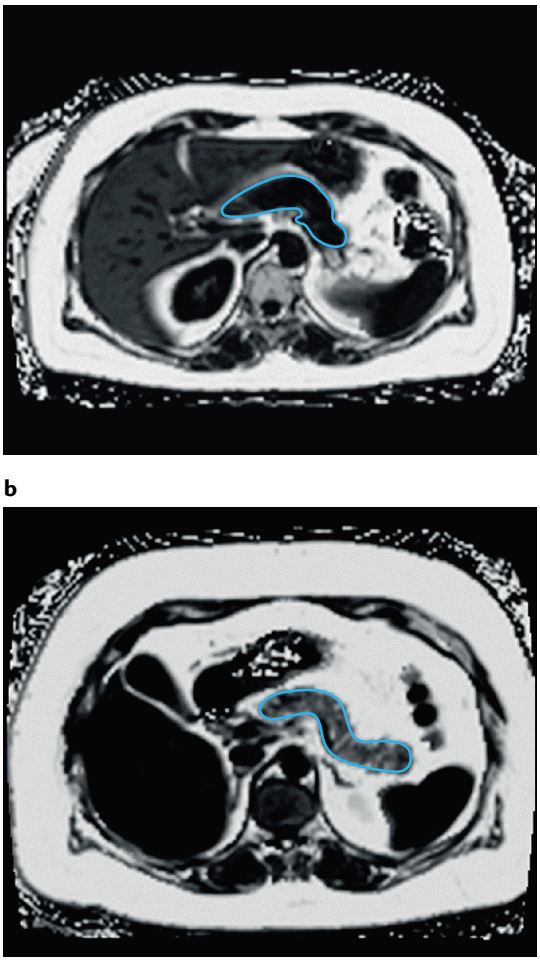

Fig. 2 | **MR tomography detection of fat accumulation in pancreatic tissue.** A patient with low (part **a**) and a patient with higher (part **b**) amounts of pancreatic fat. The images were acquired with a six-point Dixon sequence on a 3 T whole-body imager. The pancreas is outlined by the blue line in both parts **a** and **b**.

Impact of pancreatic fat accumulation

Chronic pancreatitis

Whether pancreatic fat accumulation predisposes people to chronic pancreatitis is still an open question. In a cross-sectional analysis, pancreatic fat content was increased in patients with chronic pancreatitis[95]. Similarly, a prospective cohort study found that fat accumulation is a risk factor for the development of subclinical chronic pancreatitis[96]. In both studies, the patients with chronic pancreatitis were statistically significantly older than those in the control groups. Together with other potential differences, this fact might have confounded the relationship between pancreatic fat and chronic pancreatitis.

Chronic pancreatitis can occur via mechanisms that do not involve adipocytes. During the development of obesity, however, increased levels of adipose tissue are associated with low-grade inflammation[97]. As with subcutaneous and visceral adipocytes, pancreatic adipocytes secrete cytokines, chemokines and chemoattractants. Stimulation with fatty acids and the hepatokine fetuin-A[98,99], which is an important co-factor for Toll-like receptor (TLR)-dependent signalling, increases local inflammation[20,100]. This pro-inflammatory scenario seems to be particularly relevant under certain unfavourable metabolic conditions, such as in NAFLD[101].

Pancreatic neoplasms

Several types of benign and malignant tumours originate from the pancreas. The two most common types, ductal adenocarcinoma and intraductal papillary mucinous neoplasia, seem to be more common in patients with obesity and T2DM than in metabolically healthy individuals[102]. Pancreatic ductal adenocarcinoma leads to the fourth highest mortality burden across all types of cancer[103], and the importance of understanding its causes is underlined by the lack of efficacious therapeutic options in the majority of cases.

In rodent models of pancreatic cancer and in human pancreatic specimens, pancreatic fat infiltration has been associated with adenocarcinoma[104]. Pancreatic adenocarcinoma is often preceded by intraepithelial neoplasia, which is considered a premalignant lesion[105]. Obesity and increased pancreatic fat were associated with intraepithelial neoplasia lesions in human pancreatic

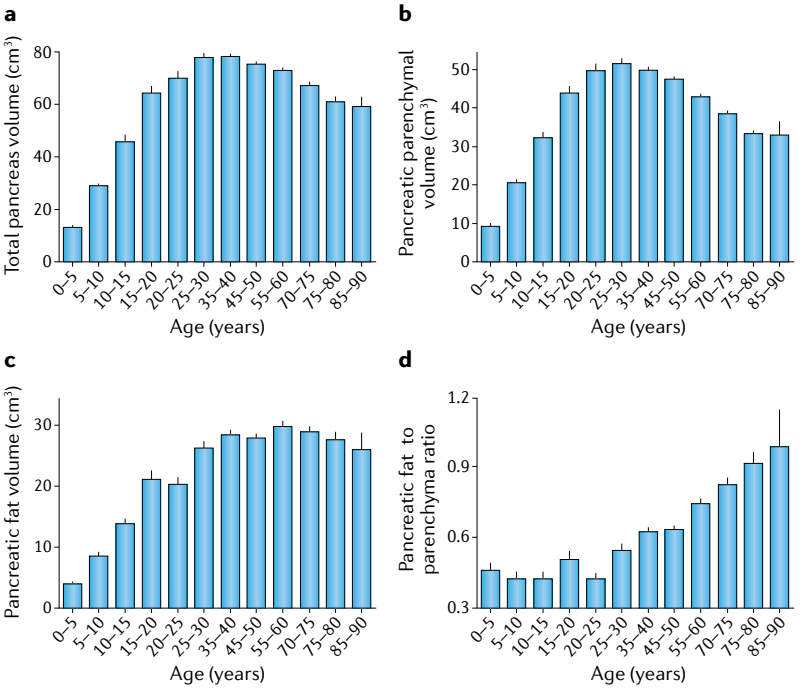

Fig. 3 | **Total, parenchymal and pancreatic fat volumes.** Calculated from CT images[29]. Total pancreas volume (part **a**). Parenchymal volume (part **b**). Fat volume (part **c**). Fat to parenchyma ratio (part **d**). Presented are means + SEM. Reprinted with permission from REF.[29], Wiley.

surgical specimens[5]. In a cancer mouse model, there was a higher incidence of intraepithelial neoplasia transforming to adenocarcinoma when the mice received a high-fat diet[106]. In patients, a high pancreatic fat content was associated with the progression of low-risk branch duct intraductal papillary mucinous neoplasias[107].

Of note, the association between pancreatic fat and pancreatic adenocarcinoma could be confounded by insulin resistance in humans, which is associated with both conditions[108]. In one large case–control study, plasma levels of adiponectin, a proxy for insulin sensitivity in adipocytes, were inversely associated with the incidence of pancreatic adenocarcinoma[109].

One possible mechanism for the link between pancreatic steatosis and premalignant and malignant lesions is that pancreatic fat might lead to an enhanced production of local cytokines, thus causing local inflammation and a predisposition to a malignant transformation of pancreatic cells[110]. This local inflammatory state could be aggravated by systemic subclinical inflammation with increased circulating levels of pro-inflammatory cytokines, as is often observed in the metabolic syndrome[111].

Disturbed glucose metabolism. Several studies have addressed the relationship between pancreatic fat and T2DM. While most studies found increased levels of fat in the pancreas of patients with T2DM[35,59,112–114], three studies did not detect such a relationship[29,115,116]. Extending cross-sectional data, a 2020 longitudinal CT study found that lean people with a fatty pancreas are more likely to develop T2DM than those without a fatty pancreas over a median follow-up of 6 years[117]. This finding opens up the possibility of using fatty pancreas as a marker of risk groups for T2DM in lean people who are otherwise metabolically inconspicuous. As the pathogenesis of T2DM is characterized by insulin resistance in combination with compromised pancreatic β-cell function, a number of studies have addressed a potential relationship between pancreatic fat and these two pathomechanisms. One of the studies did not detect any association between pancreatic fat measured using ^{1}H-MRS and insulin secretion[118] in small population samples with normal glucose tolerance and prediabetes. However, the measurements of pancreatic fat in this study have been questioned[54]. In humans with normal glucose tolerance, an association between pancreatic fat and insulin secretion has been found in some studies[119], whereas others have found no such evidence[9,31,118,120].

The partially conflicting findings with regard to pancreatic fat and insulin secretion, as well as between pancreatic fat and T2DM, could have many causes. One of the modulating factors could be the ethnic origin of study participants. Studies report differences in pancreatic fat content[9,121] and β-cell function[121] in people with mild obesity (mean BMI 30 ± 1 kg/m^2) who were of different ethnic origins. Another factor that influences the role of pancreatic fat on glycaemic traits and T2DM development could be the marked aetiological heterogeneity of T2DM. Adult-onset T2DM, as well as prediabetes, is increasingly recognized as a heterogeneous condition comprising several pathophysiologically distinct subphenotypes[122–124]. Given the apparent interaction of pancreatic fat with T2DM predisposition modelled by a genetic risk score[21], we postulate that pancreatic fat has different, possibly directionally opposing, roles across the Ahlqvist clusters of adult-onset T2DM[122]. Prospective data from a 2020 study show a clear association between high levels of pancreatic fat and T2DM in lean individuals only[117], which suggests that the subphenotype of T2DM with insulin secretion failure that is not mediated by autoimmunity (severe insulin-deficient diabetes[122]) is affected by pancreatic fat.

To date, the relationship between pancreatic fat and insulin resistance has been addressed in only two studies. Both found that pancreatic fat volume is correlated with HOMA-IR[27,113], an estimate of insulin resistance. This finding was, however, probably confounded by the relationship between the amount of visceral adipose tissue and insulin sensitivity[27]. There is accumulating evidence that pancreatic fat contributes to T2DM. In some patients, it might not only have a role in early disease development but also contribute to the progression of T2DM. However, it cannot be fully ruled out that pancreatic fat accumulates in response to other, still unknown, damage of the organ that itself causes T2DM. Whether adipocytes within the pancreatic parenchyma interfere with insulin secretion, and vice versa whether islet hormones influence adipocyte function, remain important questions.

Impaired insulin secretion

While insulin is the most important stimulus of lipogenesis and adipocyte differentiation[125], lipolysis is stimulated by glucagon[126], adrenaline and noradrenaline[125].

The innervation of islets and direct regulation of insulin secretion by sympathetic and parasympathetic neurotransmitters indicates a brain–islet hormone interaction[127,128]. It remains to be established whether adipocytes within the pancreatic parenchyma modify this crosstalk, and if pancreatic adipocytes are directly regulated by autonomic innervation.

Fat accumulation in the pancreas seems not to be detrimental for insulin secretion per se. Mouse studies have revealed that pancreatic adipocytes mediate insulin secretion by releasing fatty acids[83]. Fatty acids directly stimulate insulin secretion via free fatty acid receptor 1 (FFAR1, also known as GPR40) on β-cells[129] (FIG. 4). Co-culture of isolated islets with adipocytes (derived from either the pancreas or inguinal adipose tissue) over a period of 2 days resulted in increased insulin secretion in both the basal state (2.8 mmol/l glucose) and the stimulated state (20 mmol/l glucose). Of note, hypersecretion in response to co-culture with adipocytes was even stronger in diabetes-susceptible mice than in diabetes-resistant mice[83].

However, under certain metabolic circumstances, the fatty pancreas is accompanied by impaired insulin secretion. In the prediabetic state, increased amounts of fat in the pancreas have been linked to reduced insulin secretion, independent of multiple confounders[30,31,39]. While this association might extend to overt T2DM[113,114], it was not detected in all studies[59]. The genetic risk of T2DM could modulate the association between pancreatic fat and insulin secretion. Indeed, insulin secretion was differently associated with pancreatic fat dependent on genetic T2DM risk in our 2020 study[21]. Genetic variants that mediate insulin resistance rather than insulin secretion seem to account for this interaction. In conclusion, insulin secretion seems to be damaged by pancreatic fat in individuals with an increased genetic risk of T2DM[21] (FIG. 5).

What are the underlying mechanisms responsible for this impaired insulin secretion? Besides storing lipids, adipocytes are secretory cells that release fatty acids upon stimulation of lipolysis[125]. Furthermore, adipocytes secrete metabolites, cytokines, chemokines and adipokines[130]. These factors could negatively influence islet cell function via paracrine effects. In addition, circulating factors characteristic of the prediabetic milieu, such as the hepatokine fetuin-A and fatty acids, induce the release of pro-inflammatory chemokines and cytokines from pancreatic adipocytes via TLR4 (REFS[20,101]) (FIG. 4).

In agreement with these findings, human islets contain more CD68$^+$ macrophages and monocytes when located in proximity to pancreatic adipocytes compared with islets further away from adipocytes[20]. These immune cells release inflammatory factors that can impair β-cell function[101]. Adipocytes within pancreatic tissue could thus augment local inflammation, which could then affect β-cell function and survival. However, so far, transcriptome analyses of human islet tissue isolated by laser capture microdissection have been unable

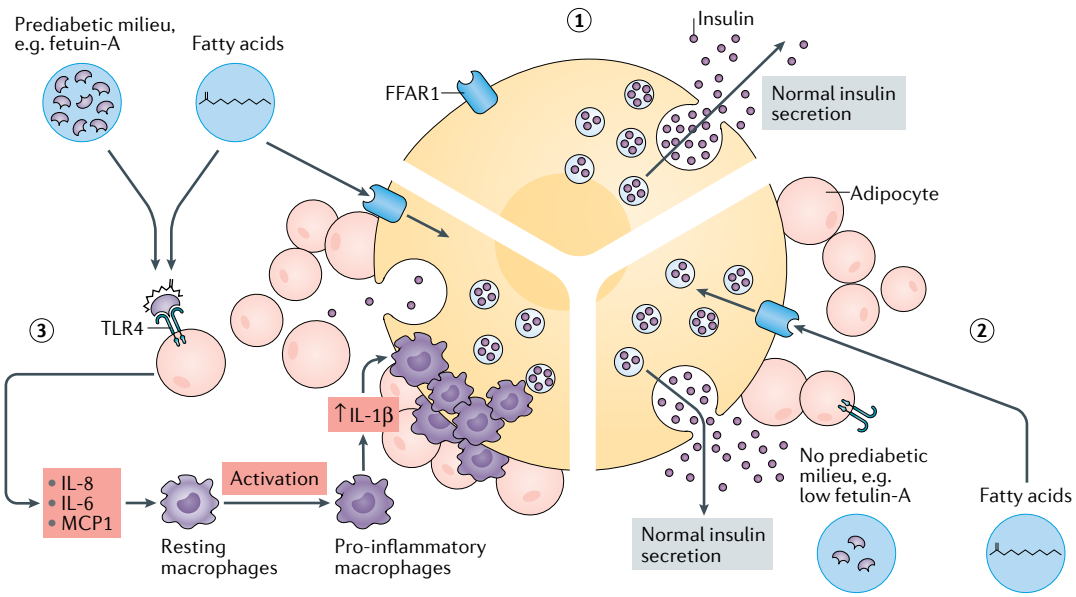

Fig. 4 | **The metabolic pattern determines the role of pancreatic fat for β-cell function.** Adipocytes and pancreatic β-cells interact under the regulation of extrapancreatic factors, with functional consequences in both cell types. In people with low amounts of fat within the pancreas (1), insulin secretion is normal. In individuals with a low genetic risk of type 2 diabetes mellitus and a healthy whole-body metabolism (2), prediabetic factors such as liver-originating fetuin-A are present only in low concentrations. Thus, the pro-inflammatory TLR4 receptor in adipocytes is not stimulated. Under these conditions, local release of fatty acids from adipocytes stimulates insulin secretion via FFAR1 (REFS[21,31,162]). However, in individuals with a genetic risk of type 2 diabetes mellitus as well as unhealthy metabolism, obesity and/or fatty liver (3), pancreatic steatosis impairs insulin secretion[21,31,74,146]. Under such metabolic circumstances, circulating factors, such as fetuin-A together with fatty acids, activate TLR4 and might thereby hamper the differentiation potential of pancreatic adipocytes[163] and alter their secretome[20]. The shift in the secretory pattern of adipocytes towards increased release of pro-inflammatory chemokines could augment immune cell infiltration, dysregulate lipolysis and impair β-cell function[20,101]. FFAR1, free fatty acid receptor 1; MCP1, monocyte chemoattractant protein-1; TLR4, Toll-like receptor 4.

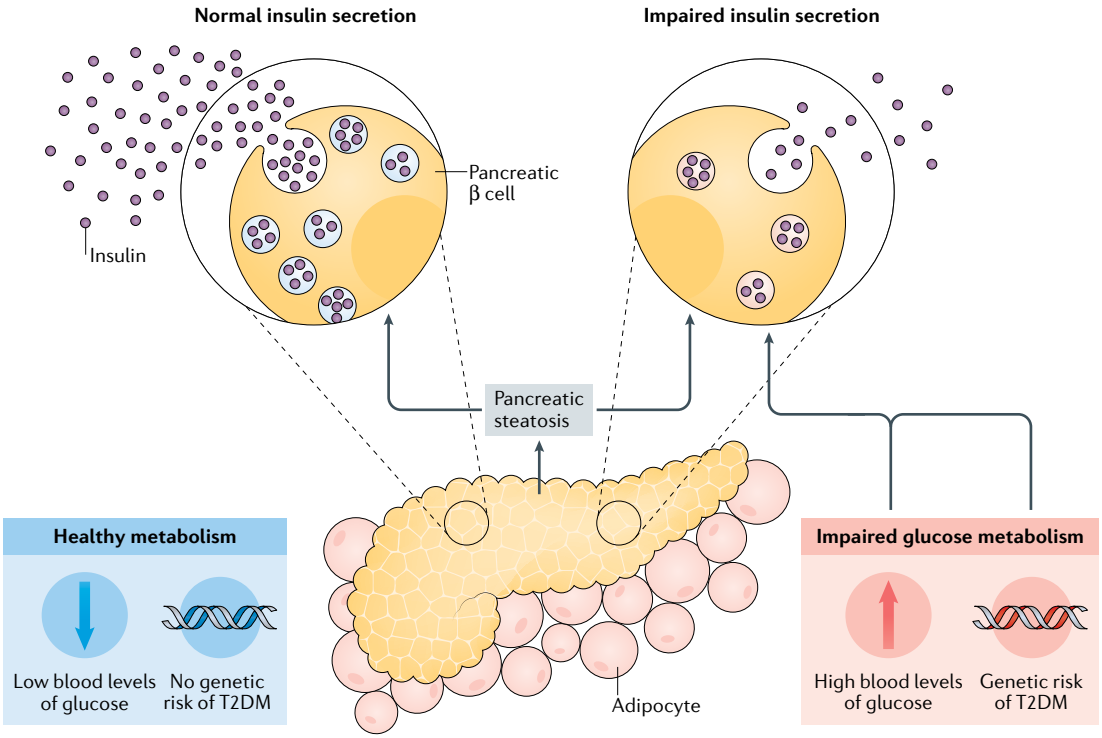

Fig. 5 | **Schematic overview of fat accumulation in the pancreas and possible metabolic consequences.** We propose the following hypothesis: if fat accumulation in the pancreas coexists with healthy glucose metabolism and no genetic risk of type 2 diabetes mellitus (T2DM), the pancreas shows normal insulin secretion; if a fatty pancreas is accompanied by impaired glucose metabolism and/or genetic risk of T2DM, insulin secretion will be impaired.

to convincingly demonstrate inflammation in pancreatic islet tissue of individuals with prediabetes and T2DM[20,131]. Further experimental evidence is required to determine the extent to which pancreatic fat accumulation changes the exposure of islets to fatty acids and whether fatty acids contribute acutely to an over-secretion of insulin or chronically to β-cell failure in humans.

Although pancreatic adipocytes account for the major part of pancreatic steatosis[17,18], triglyceride accumulation in intracellular lipid droplets within the islet endocrine cells has been detected in rat and human islets[18,132]. Intracellular triglyceride storage was associated with reduced activity of the key enzyme for glucose sensing, glucokinase, and subsequently impaired glucose-stimulated insulin secretion in rats[133–135]. In agreement with this finding, pharmacological inhibition of hormone-sensitive lipase impaired glucose-stimulated insulin secretion. Furthermore, mice with β-cell-specific knockdown of the hormone-sensitive lipase displayed altered insulin exocytosis and developed hyperglycaemia[136,137]. Further experimental evidence is required to determine the extent to which β-cells release fatty acids via lipolysis and whether fatty acids act in an autocrine fashion on β-cells.

Increased concentrations of exogenous long-chain fatty acids, such as palmitate, oleate and stearate, are now believed to differentially impact β-cells over differing periods of time. A short-term exposure to fatty acids augments glucose-stimulated insulin secretion[138], while chronically elevated levels of saturated long-chain fatty acids impair both insulin secretion and β-cell survival[139,140]. Impaired insulin secretion as a result of chronic lipid infusion for 96 h was observed in human volunteers[82]. Of note, the deleterious effect was only observed in people with a family history of T2DM, indicating that genetic background might also influence the β-cell response to long-term exposure to fatty acids. The stimulatory effect of long-chain fatty acids on insulin secretion depends on the activation of FFAR1 (REF.[141]) (FIG. 4). By contrast, the deleterious effects of chronic exposure of β-cells to saturated long-chain fatty acids are caused by intracellular changes, such as ceramide production, oxidative and ER stress, mitochondrial dysfunction and activation of stress kinases (such as JNK) and various protein kinases[142]. Protein kinase Cδ, for example, is a regulator of β-cell proliferation and survival[143,144].

Taken together, locally released fatty acids from lipid droplets in islet cells or from tissue-infiltrating adipocytes could have profound and partially divergent effects on insulin secretion. The manifold actions of fatty acids on β-cells depend on factors such as genetic background and metabolic context. This complex interplay might explain why it has been such a challenge to obtain a comprehensive understanding about these processes.

Therapies for pancreatic steatosis

Different approaches to the reduction of pancreatic fat content have been tested. Hypocaloric diets help to considerably reduce pancreatic steatosis in patients with T2DM[74,145,146]. Exercise also reduces pancreatic fat content in people with prediabetes or T2DM[147], although one small study did not detect this effect in healthy people[70]. However, the extent to which energy intake

has to be reduced and exercise increased for a meaningful reduction in pancreatic fat is still unclear. In NZO mice, the fat content in the pancreas could be statistically significantly reduced by an intermittent fasting intervention (fasting every other day), which also protected the animals from diabetes mellitus[83].

To our knowledge, only GLP1 receptor agonists have been tested for their potential to decrease fat in the pancreas as pharmacotherapy. A 6-month treatment with exenatide[148], liraglutide[149] or dulaglutide[150] did not alter pancreatic fat levels statistically significantly in patients with T2DM. However, as these treatments caused only mild weight loss in the populations of patients investigated, they might not have been potent enough to induce a reduction in pancreatic fat content.

Peroxisome proliferator-activated receptor-γ (PPARγ) agonists are antidiabetic agents with pleiotropic metabolic effects. They regulate gene transcription by activating the nuclear receptor PPARγ[151]. This activation promotes the storage of lipids in adipocytes, thereby removing these lipids from the circulation and preventing excessive fat storage in intrahepatic and visceral adipose tissue compartments[152]. A number of other effects of PPARγ agonists have been described, including preservation and/or improvement of β-cell function[153]. The PPARγ agonist rosiglitazone protects β-cells against fatty-acid-induced dysfunction[154] and reduces islet triglyceride content[155]. However, rosiglitazone has been taken off the market in parts of the world due to safety concerns[156]. Thus, a decrease in pancreatic fat content could be a possible mediator of PPARγ agonistic effects on β-cell function, but to our knowledge this has not been tested in clinical trials yet. Further studies are necessary to obtain data on feasible pharmacological approaches to the reduction of pancreatic fat.

A number of studies have analysed the effects of bariatric surgery and subsequent considerable weight loss on fat in the pancreas. All the studies found a profound reduction in pancreatic steatosis after surgery[112,145,157–159]. Interestingly, this change seems to be independent of the reduction in liver fat content[112]. Whether this beneficial effect is sustainable for a long period of time has yet to be ascertained.

All in all, these results indicate that pancreatic steatosis can be modified in vivo. Although it seems likely that a reduction in pancreatic fat could result in improved insulin metabolism, experimental evidence to this effect is still lacking. A number of associative observations indicate that β-cell function improves in response to reduced pancreatic fat after bariatric surgery[112,157], exercise[147,160,161] or low-calorie diets[74,145,146]. How changes in pancreatic steatosis affect cancer risk remains unclear. Deciphering the molecular mechanisms that mediate the negative effects of a fatty pancreas will enable clinicians to therapeutically target pancreatic steatosis in the treatment of prediabetes and T2DM, and probably also of pancreatic diseases such as cancer and pancreatitis.

Conclusions

There is growing evidence to suggest that pancreatic steatosis can introduce unfavourable effects on systemic metabolism, and it is apparently also involved in the pathogenesis of T2DM. In view of the ongoing obesity pandemic, more attention on the role of specific fat depots, such as pancreatic fat, is warranted. In particular, it will be important to identify factors that result in pancreatic fat being harmful. This knowledge could be the basis for identifying patients at risk of diabetes mellitus, who are currently not detected by conventional approaches. Evaluation of pancreatic fat content might become part of a thorough patient assessment in the future, just as assessment of liver fat is today. However, the assessment of pancreatic fat content in routine patient care requires establishment of standardized examination methods with clinically meaningful and prospectively evaluated cut-off values for fat content in the pancreas.

It is now clear that increased quantities of fatty acids within the pancreas represent a challenging environment with potential negative effects on endocrine pancreatic function. This lipid-rich environment could be either due to increased circulation of fatty acids and/or local fat accumulation in the pancreas. In addition, there is evidence that the presence of fat in the pancreas is not necessarily harmful by itself, but can induce detrimental pathomechanisms that impair endocrine functions under specific circumstances, such as prediabetes, reduced BMI and increased genetic risk of T2DM. Further basic and clinical studies that focus on these pathophysiological mechanisms could lead to new approaches to preserving or restoring β-cell function and treating T2DM.

Published online: 20 October 2021

1. Mathur, A. et al. Pancreatic steatosis promotes dissemination and lethality of pancreatic cancer. *J. Am. Coll. Surg.* **208**, 989–994 (2009).
2. Zhou, J. et al. The correlation between pancreatic steatosis and metabolic syndrome in a Chinese population. *Pancreatology* **16**, 578–583 (2016).
3. Olsen, T. S. Lipomatosis of the pancreas in autopsy material and its relation to age and overweight. *Acta Pathol. Microbiol. Scand. A* **86A**, 367–373 (1978).
One of the first analyses of the relationship between fatty pancreas with obesity in ~400 autopsies.
4. Schwenzer, N. F. et al. Quantification of pancreatic lipomatosis and liver steatosis by MRI: comparison of in/opposed-phase and spectral-spatial excitation techniques. *Invest. Radiol.* **43**, 330–337 (2008).
5. Rebours, V. et al. Obesity and fatty pancreatic infiltration are risk factors for pancreatic precancerous lesions (PanIN). *Clin. Cancer Res.* **21**, 3522–3528 (2015).
6. Wang, H., Maitra, A. & Wang, H. Obesity, intrapancreatic fatty infiltration, and pancreatic cancer. *Clin. Cancer Res.* **21**, 3369–3371 (2015).
7. Mathur, A. et al. Nonalcoholic fatty pancreas disease. *HPB* **9**, 312–318 (2007).
8. Targher, G. et al. Pancreatic fat accumulation and its relationship with liver fat content and other fat depots in obese individuals. *J. Endocrinol. Invest.* **35**, 748–753 (2012).
9. Lê, K.-A. et al. Ethnic differences in pancreatic fat accumulation and its relationship with other fat depots and inflammatory markers. *Diabetes Care* **34**, 485–490 (2011).
This work describes ethnic differences in pancreatic fat and associates it with clinical features.
10. Smits, M. M. & van Geenen, E. J. M. The clinical significance of pancreatic steatosis. *Nat. Rev. Gastroenterol. Hepatol.* **8**, 169–177 (2011).
11. Wang, C.-Y., Ou, H.-Y., Chen, M.-F., Chang, T.-C. & Chang, C.-J. Enigmatic ectopic fat: prevalence of nonalcoholic fatty pancreas disease and its associated factors in a Chinese population. *J. Am. Heart Assoc.* **3**, e000297 (2014).
12. Wong, V. W.-S. et al. Fatty pancreas, insulin resistance, and β-cell function: a population study using fat-water magnetic resonance imaging. *Am. J. Gastroenterol.* **109**, 589–597 (2014).
13. Lesmana, C. R. A., Pakasi, L. S., Inggriani, S., Aidawati, M. L. & Lesmana, L. A. Prevalence of non-alcoholic fatty pancreas disease (NAFPD) and its risk factors among adult medical check-up patients in a private hospital: a large cross sectional study. *BMC Gastroenterol.* **15**, 174 (2015).
14. Sepe, P. S. et al. A prospective evaluation of fatty pancreas by using EUS. *Gastrointest. Endosc.* **73**, 987–993 (2011).
This works identified pancreatic fat in a large number of patients using endoscopic ultrasonography and described a strong association with the metabolic syndrome.

15. Walters, M. N.-I. Adipose atrophy of the exocrine pancreas. *J. Pathol. Bacteriol.* **92**, 547–557 (1966).
16. Molnar, L., Kerekes, E. & Meszaros, A. Significance of the fatty infiltration of the pancreas [Hungarian]. *Orv. Hetil.* **99**, 1243–1246 (1958).
This is one of the first systematic descriptions of fatty pancreas identified in 47% of 250 autopsies.
17. Rosengren, A. H. et al. Reduced insulin exocytosis in human pancreatic β-cells with gene variants linked to type 2 diabetes. *Diabetes* **61**, 1726–1733 (2012).
18. Tong, X. et al. Lipid droplet accumulation in human pancreatic islets is dependent on both donor age and health. *Diabetes* **69**, 342–354 (2020).
19. Ionescu-Tirgoviste, C. et al. A 3D map of the islet routes throughout the healthy human pancreas. *Sci. Rep.* **5**, 14634 (2015).
20. Gerst, F. et al. Metabolic crosstalk between fatty pancreas and fatty liver: effects on local inflammation and insulin secretion. *Diabetologia* **60**, 2240–2251 (2017).
This is the first evidence that fetuin-A can mediate a metabolic crosstalk between liver fat, insulin resistance and pancreatic fat exacerbating local inflammation in the pancreas and leading to decreased insulin secretion.
21. Wagner, R. et al. Pancreatic steatosis associates with impaired insulin secretion in genetically predisposed individuals. *J. Clin. Endocrinol. Metab.* **105**, 3518–3525 (2020).
This study demonstrates that the link between fatty pancreas and impaired insulin secretion depends on genetic risk of type 2 diabetes mellitus.
22. Barroso Oquendo, M. et al. Pancreatic fat cells of humans with type 2 diabetes display reduced adipogenic and lipolytic activity. *Am. J. Physiol. Cell Physiol.* **320**, C1000–C1012 (2021).
23. Go, V. L. W. et al. *The Pancreas: Biology, Pathobiology, and Disease* (Lippincott Williams & Wilkins, 1993).
24. Nakamura, T. et al. Cotton rat (Sigmodon hispidus) develops metabolic disorders associated with visceral adipose inflammation and fatty pancreas without obesity. *Cell Tissue Res.* **375**, 483–492 (2019).
25. Patel, S., Bellon, E. M., Haaga, J. & Park, C. H. Fat replacement of the exocrine pancreas. *AJR Am. J. Roentgenol.* **135**, 843–845 (1980).
26. Murakami, R. et al. Pancreas fat and β cell mass in humans with and without diabetes: an analysis in the Japanese population. *J. Clin. Endocrinol. Metab.* **102**, 3251–3260 (2017).
27. Lee, J. S. et al. Clinical implications of fatty pancreas: correlations between fatty pancreas and metabolic syndrome. *World J. Gastroenterol.* **15**, 1869–1875 (2009).
28. Al-Haddad, M. et al. Risk factors for hyperechogenic pancreas on endoscopic ultrasound: a case-control study. *Pancreas* **38**, 672–675 (2009).
29. Saisho, Y. et al. Pancreas volumes in humans from birth to age one hundred taking into account sex, obesity, and presence of type-2 diabetes. *Clin. Anat.* **20**, 933–942 (2007).
The study provides a systematic description of changes in pancreas anatomy across the human lifespan.
30. Zijl, V. D. et al. Ectopic fat storage in the pancreas, liver, and abdominal fat depots: impact on β-cell function in individuals with impaired glucose metabolism. *J. Clin. Endocrinol. Metab.* **96**, 459–467 (2011).
31. Heni, M. et al. Pancreatic fat is negatively associated with insulin secretion in individuals with impaired fasting glucose and/or impaired glucose tolerance: a nuclear magnetic resonance study. *Diabetes Metab. Res. Rev.* **26**, 200–205 (2010).
This work finds that pancreatic fat impacts insulin secretion in patients with prediabetes, but not in those with normal glucose tolerance.
32. Wu, W.-C. & Wang, C.-Y. Association between non-alcoholic fatty pancreatic disease (NAFPD) and the metabolic syndrome: case–control retrospective study. *Cardiovasc. Diabetol.* **12**, 77 (2013).
33. Weng, S. et al. Prevalence and factors associated with nonalcoholic fatty pancreas disease and its severity in China. *Medicine* **97**, e11293 (2018).
34. Hung, C.-S. et al. Increased pancreatic echogenicity with US: relationship to glycemic progression and incident diabetes. *Radiology* **287**, 853–863 (2018).
This paper describes the relationship between ultrasound-detected fatty pancreas and diabetes mellitus in approximately 32,000 participants.
35. Ou, H.-Y., Wang, C.-Y., Yang, Y.-C., Chen, M.-F. & Chang, C.-J. The association between nonalcoholic fatty pancreas disease and diabetes. *PLoS ONE* **8**, e62561 (2013).
36. Johnson, M. L. & Mack, L. A. Ultrasonic evaluation of the pancreas. *Gastrointest. Radiol.* **3**, 257–266 (1978).
37. Lindsell, D. R. M. Ultrasound imaging of pancreas and biliary tract. *Lancet* **335**, 390–393 (1990).
38. Choi, C. W. et al. Associated factors for a hyperechogenic pancreas on endoscopic ultrasound. *World J. Gastroenterol.* **16**, 4329–4334 (2010).
39. Yamazaki, H. et al. Independent association between prediabetes and future pancreatic fat accumulation: a 5-year Japanese cohort study. *J. Gastroenterol.* **53**, 873–882 (2018).
40. Kim, S. Y. et al. Quantitative assessment of pancreatic fat by using unenhanced CT: pathologic correlation and clinical implications. *Radiology* **271**, 104–112 (2014).
41. Hong, C. W., Fazeli Dehkordy, S., Hooker, J. C., Hamilton, G. & Sirlin, C. B. Fat quantification in the abdomen. *Top. Magn. Reson. Imaging* **26**, 221–227 (2017).
42. Kashiwagi, K. et al. Pancreatic fat content detected by computed tomography and its significant relationship with intraductal papillary mucinous neoplasm. *Pancreas* **47**, 1087–1092 (2018).
43. Hu, H. H., Kim, H.-W., Nayak, K. S. & Goran, M. I. Comparison of fat-water MRI and single-voxel MRS in the assessment of hepatic and pancreatic fat fractions in humans. *Obesity* **18**, 841–847 (2010).
44. Al-Mrabeh, A., Hollingsworth, K. G., Steven, S., Tiniakos, D. & Taylor, R. Quantification of intrapancreatic fat in type 2 diabetes by MRI. *PLoS ONE* **12**, e0174660 (2017).
45. Sakai, N. S., Taylor, S. A. & Chouhan, M. D. Obesity, metabolic disease and the pancreas–quantitative imaging of pancreatic fat. *Br. J. Radiol.* **91**, 20180267 (2018).
46. Dixon, W. T. Simple proton spectroscopic imaging. *Radiology* **153**, 189–194 (1984).
47. Sarma, M. K. et al. Noninvasive assessment of abdominal adipose tissues and quantification of hepatic and pancreatic fat fractions in type 2 diabetes mellitus. *Magn. Reson. Imaging* **72**, 95–102 (2020).
48. Heber, S. D. et al. Pancreatic fat content by magnetic resonance imaging in subjects with prediabetes, diabetes, and controls from a general population without cardiovascular disease. *PLoS ONE* **12**, e0177154 (2017).
49. Hernando, D. et al. Multisite, multivendor validation of the accuracy and reproducibility of proton-density fat-fraction quantification at 1.5T and 3T using a fat-water phantom. *Magn. Reson. Med.* **77**, 1516–1524 (2017).
50. Hu, H. H. et al. Linearity and bias of proton density fat fraction as a quantitative imaging biomarker: a multicenter, multiplatform, multivendor phantom study. *Radiology* **298**, 640–651 (2021).
51. Meisamy, S. et al. Quantification of hepatic steatosis with T1-independent, T2-corrected MR imaging with spectral modeling of fat: blinded comparison with MR spectroscopy. *Radiology* **258**, 767–775 (2011).
52. Kukuk, G. M. et al. Comparison between modified Dixon MRI techniques, MR spectroscopic relaxometry, and different histologic quantification methods in the assessment of hepatic steatosis. *Eur. Radiol.* **25**, 2869–2879 (2015).
53. Zhong, X. et al. Liver fat quantification using a multi-step adaptive fitting approach with multi-echo GRE imaging. *Magn. Reson. Med.* **72**, 1353–1365 (2014).
54. Hollingsworth, K. G., Al-Mrabeh, A., Steven, S. & Taylor, R. Pancreatic triacylglycerol distribution in type 2 diabetes. *Diabetologia* **58**, 2676–2678 (2015).
55. Fukui, H. et al. Evaluation of fatty pancreas by proton density fat fraction using 3-T magnetic resonance imaging and its association with pancreatic cancer. *Eur. J. Radiol.* **118**, 25–31 (2019).
56. Yoon, J. H. et al. Pancreatic steatosis and fibrosis: quantitative assessment with preoperative multiparametric MR imaging. *Radiology* **279**, 140–150 (2016).
57. Hakim, O. et al. Associations between pancreatic lipids and β-cell function in black African and white European men with type 2 diabetes. *J. Clin. Endocrinol. Metab.* **104**, 1201–1210 (2019).
58. Kato, S. et al. Three-dimensional analysis of pancreatic fat by fat-water magnetic resonance imaging provides detailed characterization of pancreatic steatosis with improved reproducibility. *PLoS ONE* **14**, e0224921 (2019).
59. Tushuizen, M. E. et al. Pancreatic fat content and β-cell function in men with and without type 2 diabetes. *Diabetes Care* **30**, 2916–2921 (2007).
This is one of the first reports of the potential detrimental impact of fatty pancreas on β-cell function.
60. Machann, J. et al. Morning to evening changes of intramyocellular lipid content in dependence on nutrition and physical activity during one single day: a volume selective 1H-MRS study. *MAGMA* **24**, 29–33 (2011).
61. Colgan, T. J., Van Pay, A. J., Sharma, S. D., Mao, L. & Reeder, S. B. Diurnal variation of proton density fat fraction in the liver using quantitative chemical shift encoded MRI. *J. Magn. Reson. Imaging* **51**, 407–414 (2020).
62. Machann, J. et al. Short-term variability of proton density fat fraction in pancreas and liver assessed by multi-echo chemical-shift encoding-based MRI at 3T. *medRxiv* https://doi.org/10.1101/2021.06.08.21257560 (2021).
63. Staaf, J. et al. Pancreatic fat is associated with metabolic syndrome and visceral fat but not beta-cell function or body mass index in pediatric obesity. *Pancreas* **46**, 358–365 (2017).
64. Yamazaki, H. et al. Association between pancreatic fat and incidence of metabolic syndrome: a 5-year Japanese cohort study. *J. Gastroenterol. Hepatol.* **33**, 2048–2054 (2018).
65. Lingvay, I. et al. Noninvasive quantification of pancreatic fat in humans. *J. Clin. Endocrinol. Metab.* **94**, 4070–4076 (2009).
66. Rossi, A. P. et al. Predictors of ectopic fat accumulation in liver and pancreas in obese men and women. *Obesity* **19**, 1747–1754 (2011).
67. Jaghutriz, B. A. et al. Metabolomic characteristics of fatty pancreas. *Exp. Clin. Endocrinol. Diabetes* **128**, 804–810 (2020).
68. Maggio, A. B. R. et al. Increased pancreatic fat fraction is present in obese adolescents with metabolic syndrome. *J. Pediatr. Gastroenterol. Nutr.* **54**, 720–726 (2012).
69. Patel, N. S. et al. Insulin resistance increases MRI-estimated pancreatic fat in nonalcoholic fatty liver disease and normal controls. *Gastroenterol. Res. Pract.* **2013**, 498296 (2013).
70. Hannukainen, J. C. et al. Liver and pancreatic fat content and metabolism in healthy monozygotic twins with discordant physical activity. *J. Hepatol.* **54**, 545–552 (2011).
71. van Geenen, E.-J. M. et al. Nonalcoholic fatty liver disease is related to nonalcoholic fatty pancreas disease. *Pancreas* **39**, 1185–1190 (2010).
72. Milovanovic, T. et al. Ultrasonographic evaluation of fatty pancreas in Serbian patients with non alcoholic fatty liver disease–a cross sectional study. *Medicina* **55**, 697 (2019).
73. Taylor, R. Pathogenesis of type 2 diabetes: tracing the reverse route from cure to cause. *Diabetologia* **51**, 1781–1789 (2008).
74. Taylor, R. et al. Remission of human type 2 diabetes requires decrease in liver and pancreas fat content but is dependent upon capacity for β cell recovery. *Cell Metab.* **28**, 547–556.e3 (2018).
This study demonstrates that fatty pancreas is reversible by a hypocaloric diet.
75. Al-Mrabeh, A. et al. Hepatic lipoprotein export and remission of human type 2 diabetes after weight loss. *Cell Metab.* **31**, 233–249.e4 (2020).
This study shows that changes in pancreatic fat are related to changes in β-cell function after weight loss.
76. Donnelly, K. L. et al. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. *J. Clin. Invest.* **115**, 1343–1351 (2005).
77. Yadav, D. & Whitcomb, D. C. The role of alcohol and smoking in pancreatitis. *Nat. Rev. Gastroenterol. Hepatol.* **7**, 131–145 (2010).
78. Apte, M. V., Pirola, R. C. & Wilson, J. S. Mechanisms of alcoholic pancreatitis. *J. Gastroenterol. Hepatol.* **25**, 1816–1826 (2010).
79. Crane, J. D. et al. ELBW survivors in early adulthood have higher hepatic, pancreatic and subcutaneous fat. *Sci. Rep.* **6**, 31560 (2016).
80. Curhan Gary, C. et al. Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. *Circulation* **94**, 3246–3250 (1996).
81. Raeder, H. et al. Pancreatic lipomatosis is a structural marker in nondiabetic children with mutations in carboxyl-ester lipase. *Diabetes* **56**, 444–449 (2007).
82. Kashyap, S. et al. A sustained increase in plasma free fatty acids impairs insulin secretion in nondiabetic subjects genetically predisposed to develop type 2 diabetes. *Diabetes* **52**, 2461–2474 (2003).

83. Quiclet, C. et al. Pancreatic adipocytes mediate hypersecretion of insulin in diabetes-susceptible mice. *Metabolism* **97**, 9–17 (2019).
This is a study in mice that suggests that intermittent fasting prevents fatty pancreas.
84. Kleinert, M. et al. Animal models of obesity and diabetes mellitus. *Nat. Rev. Endocrinol.* **14**, 140–162 (2018).
85. Engjom, T. et al. Sonographic pancreas echogenicity in cystic fibrosis compared to exocrine pancreatic function and pancreas fat content at Dixon-MRI. *PLoS ONE* **13**, e0201019 (2018).
86. Feigelson, J. et al. Imaging changes in the pancreas in cystic fibrosis: a retrospective evaluation of 55 cases seen over a period of 9 years. *J. Pediatr. Gastroenterol. Nutr.* **30**, 145–151 (2000).
87. Soyer, P. et al. Cystic fibrosis in adolescents and adults: fatty replacement of the pancreas–CT evaluation and functional correlation. *Radiology* **210**, 611–615 (1999).
88. Tham, R. T. et al. Cystic fibrosis: MR imaging of the pancreas. *Radiology* **179**, 183–186 (1991).
89. Toiviainen-Salo, S. et al. Magnetic resonance imaging findings of the pancreas in patients with Shwachman-Diamond syndrome and mutations in the SBDS gene. *J. Pediatr.* **152**, 434–436 (2008).
90. Argyropoulou, M. I. et al. Liver, bone marrow, pancreas and pituitary gland iron overload in young and adult thalassemic patients: a T2 relaxometry study. *Eur. Radiol.* **17**, 3025–3030 (2007).
91. Midiri, M. et al. MR imaging of pancreatic changes in patients with transfusion-dependent beta-thalassemia major. *Am. J. Roentgenol.* **173**, 187–192 (1999).
92. Papakonstantinou, O. et al. The pancreas in β-thalassemia major: MR imaging features and correlation with iron stores and glucose disturbances. *Eur. Radiol.* **17**, 1535–1543 (2007).
93. Pfeifer, C. D. et al. Pancreatic iron and fat assessment by MRI-R2* in patients with iron overload diseases. *J. Magn. Reson. Imaging* **42**, 196–203 (2015).
94. Katz, D. et al. Using CT to reveal fat-containing abnormalities of the pancreas. *Am. J. Roentgenol.* **172**, 393–396 (1999).
95. Tirkes, T. et al. Association of pancreatic steatosis with chronic pancreatitis, obesity, and type 2 diabetes mellitus. *Pancreas* **48**, 420–426 (2019).
96. Fujii, M., Ohno, Y., Yamada, M., Kamada, Y. & Miyoshi, E. Impact of fatty pancreas and lifestyle on the development of subclinical chronic pancreatitis in healthy people undergoing a medical checkup. *Environ. Health Prev. Med.* **24**, 10 (2019).
97. Saltiel, A. R. & Olefsky, J. M. Inflammatory mechanisms linking obesity and metabolic disease. *J. Clin. Invest.* **127**, 1–4 (2017).
98. Pal, D. et al. Fetuin-A acts as an endogenous ligand of TLR4 to promote lipid-induced insulin resistance. *Nat. Med.* **18**, 1279–1285 (2012).
99. Stefan, N. & Häring, H.-U. Circulating fetuin-A and free fatty acids interact to predict insulin resistance in humans. *Nat. Med.* **19**, 394–395 (2013).
This study describes the interaction of fetuin-A and fatty acids on insulin resistance in humans.
100. Siegel-Axel, D. I. et al. Fetuin-A influences vascular cell growth and production of proinflammatory and angiogenic proteins by human perivascular fat cells. *Diabetologia* **57**, 1057–1066 (2014).
101. Gerst, F. et al. What role do fat cells play in pancreatic tissue? *Mol. Metab.* **25**, 1–10 (2019).
102. Michaud, D. S. et al. Physical activity, obesity, height, and the risk of pancreatic cancer. *JAMA* **286**, 921–929 (2001).
103. Maisonneuve, P. Epidemiology and burden of pancreatic cancer. *La. Presse Méd.* **48**, e113–e123 (2019).
104. Takahashi, M. et al. Fatty pancreas: a possible risk factor for pancreatic cancer in animals and humans. *Cancer Sci.* **109**, 3013–3023 (2018).
105. Yu, D.-Y. et al. Clinical significance of pancreatic intraepithelial neoplasia in resectable pancreatic cancer on survivals. *Ann. Surg. Treat. Res.* **94**, 247–253 (2018).
106. Chang, H.-H. et al. Incidence of pancreatic cancer is dramatically increased by a high fat, high calorie diet in KrasG12D mice. *PLoS ONE* **12**, e0184455 (2017).
107. Kashiwagi, K. et al. Pancreatic fat content may increase the risk of imaging progression in low-risk branch duct intraductal papillary mucinous neoplasm. *J. Dig. Dis.* **20**, 557–562 (2019).
108. Stolzenberg-Solomon, R. Z. et al. Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. *JAMA* **294**, 2872–2878 (2005).
109. Bao, Y. et al. A prospective study of plasma adiponectin and pancreatic cancer risk in five US cohorts. *J. Natl Cancer Inst.* **105**, 95–103 (2013).
110. Roshani, R., McCarthy, F. & Hagemann, T. Inflammatory cytokines in human pancreatic cancer. *Cancer Lett.* **345**, 157–163 (2014).
111. Wisse, B. E. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. *JASN* **15**, 2792–2800 (2004).
112. Gaborit, B. et al. Ectopic fat storage in the pancreas using ^{1}H-MRS: importance of diabetic status and modulation with bariatric surgery-induced weight loss. *Int. J. Obes.* **39**, 480–487 (2015).
113. Lu, T. et al. Pancreatic fat content is associated with β-cell function and insulin resistance in Chinese type 2 diabetes subjects. *Endocr. J.* **66**, 265–270 (2019).
114. Chin, S. O. et al. Pancreatic fat accumulation is associated with decreased β-cell function and deterioration in glucose tolerance in Korean adults. *Diabetes Metab. Res. Rev.* https://doi.org/10.1002/dmrr.3425 (2020).
115. Kühn, J.-P. et al. Pancreatic steatosis demonstrated at MR imaging in the general population: clinical relevance. *Radiology* **276**, 129–136 (2015).
116. Yamazaki, H. et al. Lack of independent association between fatty pancreas and incidence of type 2 diabetes: 5-year Japanese cohort study. *Diabetes Care* **39**, 1677–1683 (2016).
117. Yamazaki, H. et al. Longitudinal association of fatty pancreas with the incidence of type-2 diabetes in lean individuals: a 6-year computed tomography-based cohort study. *J. Gastroenterol.* **55**, 712–721 (2020).
This study demonstrates that fatty pancreas predicts future type 2 diabetes mellitus in lean people.
118. Begovatz, P. et al. Pancreatic adipose tissue infiltration, parenchymal steatosis and beta cell function in humans. *Diabetologia* **58**, 1646–1655 (2015).
119. Roh, E. et al. Comparison of pancreatic volume and fat amount linked with glucose homeostasis between healthy Caucasians and Koreans. *Diabetes Obes. Metab.* **20**, 2642–2652 (2018).
120. Nowotny, B. et al. Circulating triacylglycerols but not pancreatic fat associate with insulin secretion in healthy humans. *Metab. Clin. Exp.* **81**, 113–125 (2018).
121. Szczepaniak, L. S. et al. Pancreatic steatosis and its relationship to β-cell dysfunction in humans: racial and ethnic variations. *Diabetes Care* **35**, 2377–2383 (2012).
122. Ahlqvist, E. et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol.* **6**, 361–369 (2018).
This study characterizes sub-phenotypes of type 2 diabetes mellitus and their clinical relevance.
123. Wagner, R. & Fritsche, A. Reclassification of diabetes mellitus based on pathophysiologic and genetic features [German]. *Dtsch. Med. Wochenschr.* **145**, 601–608 (2020).
124. Wagner, R. et al. Pathophysiology-based subphenotyping of individuals at elevated risk for type 2 diabetes. *Nat. Med.* **27**, 49–57 (2021).
This study characterizes sub-phenotypes of people at risk of type 2 diabetes mellitus and their prospective clinical value.
125. Duncan, R. E., Ahmadian, M., Jaworski, K., Sarkadi-Nagy, E. & Sul, H. S. Regulation of lipolysis in adipocytes. *Annu. Rev. Nutr.* **27**, 79–101 (2007).
126. Perea, A., Clemente, F., Martinell, J., Villanueva-Peñacarrillo, M. L. & Valverde, I. Physiological effect of glucagon in human isolated adipocytes. *Horm. Metab. Res.* **27**, 372–375 (1995).
127. Heni, M. et al. Insulin action in the hypothalamus increases second-phase insulin secretion in humans. *Neuroendocrinology* **110**, 929–937 (2020).
This work demonstrates that the brain is able to modulate insulin secretion in humans.
128. Thorens, B. Neural regulation of pancreatic islet cell mass and function. *Diabetes Obes. Metab.* **16**, 87–95 (2014).
129. Wagner, R. et al. Reevaluation of fatty acid receptor 1 as a drug target for the stimulation of insulin secretion in humans. *Diabetes* **62**, 2106–2111 (2013).
130. Rodríguez, A., Ezquerro, S., Méndez-Giménez, L., Becerril, S. & Frühbeck, G. Revisiting the adipocyte: a model for integration of cytokine signaling in the regulation of energy metabolism. *Am. J. Physiol. Endocrinol. Metab.* **309**, E691–E714 (2015).
131. Solimena, M. et al. Systems biology of the IMIDIA biobank from organ donors and pancreatectomised patients defines a novel transcriptomic signature of islets from individuals with type 2 diabetes. *Diabetologia* **61**, 641–657 (2018).
132. Man, Z. W. et al. Impaired beta-cell function and deposition of fat droplets in the pancreas as a consequence of hypertriglyceridemia in OLETF rat, a model of spontaneous NIDDM. *Diabetes* **46**, 1718–1724 (1997).
133. Winzell, M. S., Ström, K., Holm, C. & Ahrén, B. Glucose-stimulated insulin secretion correlates with β-cell lipolysis. *Nutr. Metab. Cardiovasc. Dis.* **16**, S11–S16 (2006).
134. Nolan, C. J. et al. Beta cell compensation for insulin resistance in Zucker fatty rats: increased lipolysis and fatty acid signalling. *Diabetologia* **49**, 2120–2130 (2006).
135. Cantley, J. et al. Deletion of PKCε selectively enhances the amplifying pathways of glucose-stimulated insulin secretion via increased lipolysis in mouse β-cells. *Diabetes* **58**, 1826–1834 (2009).
136. Mulder, H., Yang, S., Winzell, M. S., Holm, C. & Ahrén, B. Inhibition of lipase activity and lipolysis in rat islets reduces insulin secretion. *Diabetes* **53**, 122–128 (2004).
This work describes the impact of β-cell lipid metabolism on insulin secretion.
137. Fex, M. et al. A beta cell-specific knockout of hormone-sensitive lipase in mice results in hyperglycaemia and disruption of exocytosis. *Diabetologia* **52**, 271–280 (2009).
138. Beysen, C. et al. Interaction between specific fatty acids, GLP-1 and insulin secretion in humans. *Diabetologia* **45**, 1533–1541 (2002).
139. Eitel, K. et al. Protein kinase C δ activation and translocation to the nucleus are required for fatty acid-induced apoptosis of insulin-secreting cells. *Diabetes* **52**, 991–997 (2003).
140. Lupi, R. et al. Prolonged exposure to free fatty acids has cytostatic and pro-apoptotic effects on human pancreatic islets: evidence that β-cell death is caspase mediated, partially dependent on ceramide pathway, and Bcl-2 regulated. *Diabetes* **51**, 1437–1442 (2002).
141. Latour, M. G. et al. GPR40 is necessary but not sufficient for fatty acid stimulation of insulin secretion in vivo. *Diabetes* **56**, 1087–1094 (2007).
142. Schmitz-Peiffer, C. & Biden, T. J. PKCδ blues for the β-cell. *Diabetes* **59**, 1–3 (2010).
143. Hennige, A. M. et al. Overexpression of kinase-negative protein kinase Cδ in pancreatic β-cells protects mice from diet-induced glucose intolerance and β-cell dysfunction. *Diabetes* **59**, 119–127 (2010).
144. Ranta, F. et al. Protein kinase C delta (PKCδ) affects proliferation of insulin-secreting cells by promoting nuclear extrusion of the cell cycle inhibitor p21Cip1/WAF1. *PLoS ONE* **6**, e28828 (2011).
145. Steven, S. et al. Weight loss decreases excess pancreatic triacylglycerol specifically in type 2 diabetes. *Diabetes Care* **39**, 158–165 (2016).
146. Lim, E. L. et al. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* **54**, 2506–2514 (2011).
147. Heiskanen, M. A. et al. Exercise training decreases pancreatic fat content and improves beta cell function regardless of baseline glucose tolerance: a randomised controlled trial. *Diabetologia* **61**, 1817–1828 (2018).
148. Dutour, A. et al. Exenatide decreases liver fat content and epicardial adipose tissue in patients with obesity and type 2 diabetes: a prospective randomized clinical trial using magnetic resonance imaging and spectroscopy. *Diabetes Obes. Metab.* **18**, 882–891 (2016).
149. Vanderheiden, A. et al. Mechanisms of action of liraglutide in patients with type 2 diabetes treated with high-dose insulin. *J. Clin. Endocrinol. Metab.* **101**, 1798–1806 (2016).
150. Kuchay, M. S. et al. Effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD: randomised controlled trial (D-LIFT trial). *Diabetologia* **63**, 2434–2445 (2020).
151. Yki-Järvinen, H. Thiazolidinediones. *N. Engl. J. Med.* **351**, 1106–1118 (2004).
152. Gastaldelli, A. et al. Decreased whole body lipolysis as a mechanism of the lipid-lowering effect of pioglitazone in type 2 diabetic patients. *Am. J. Physiol. Endocrinol. Metab.* **297**, E225–E230 (2009).
153. Eldor, R., DeFronzo, R. A. & Abdul-Ghani, M. In vivo actions of peroxisome Proliferator-activated receptors: glycemic control, insulin sensitivity, and insulin secretion. *Diabetes Care* **36**, S162–S174 (2013).

154. Lupi, R. et al. Rosiglitazone prevents the impairment of human islet function induced by fatty acids: evidence for a role of PPARγ2 in the modulation of insulin secretion. *Am. J. Physiol. Endocrinol. Metab.* **286**, E560–E567 (2004).
155. Matsui, J. et al. Pioglitazone reduces islet triglyceride content and restores impaired glucose-stimulated insulin secretion in heterozygous peroxisome proliferator-activated receptor-γ-deficient mice on a high-fat diet. *Diabetes* **53**, 2844–2854 (2004).
156. Nissen, S. E. The rise and fall of rosiglitazone. *Eur. Heart J.* **31**, 773–776 (2010).
157. Honka, H. et al. The effects of bariatric surgery on pancreatic lipid metabolism and blood flow. *J. Clin. Endocrinol. Metab.* **100**, 2015–2023 (2015).
This work shows the effect of bariatric surgery on pancreatic fat and a possible link to improved glucose metabolism.
158. Umemura, A. et al. Pancreas volume reduction and metabolic effects in Japanese patients with severe obesity following laparoscopic sleeve gastrectomy. *Endocr. J.* **64**, 487–498 (2017).
159. Hui, S. C. N. et al. Observed changes in brown, white, hepatic and pancreatic fat after bariatric surgery: evaluation with MRI. *Eur. Radiol.* **29**, 849–856 (2019).
160. Slentz, C. A. et al. Effects of exercise training intensity on pancreatic β-cell function. *Diabetes Care* **32**, 1807–1811 (2009).
161. Solomon, T. P. J. et al. Pancreatic β-cell function is a stronger predictor of changes in glycemic control after an aerobic exercise intervention than insulin sensitivity. *J. Clin. Endocrinol. Metab.* **98**, 4176–4186 (2013).
162. Cen, J., Sargsyan, E. & Bergsten, P. Fatty acids stimulate insulin secretion from human pancreatic islets at fasting glucose concentrations via mitochondria-dependent and -independent mechanisms. *Nutr. Metab.* **13**, 59 (2016).
163. Dasgupta, S. et al. NF-κB mediates lipi d-induced fetuin-A expression in hepatocytes that impairs adipocyte function effecting insulin resistance. *Biochem. J.* **429**, 451–462 (2010).

Acknowledgements
We thank S. Hülskämper (University of Tübingen) for artistic support in preparation of the first drafts of the figures. The authors acknowledge support (grant no. 01GI0925) from the Federal Ministry of Education and Research (BMBF) to the German Center for Diabetes Research (DZD). The authors also acknowledge the support from JSPS KAKENHI (grant no. 19K16978).

Author contributions
M.H., R.W. and S.S.E. contributed to all aspects of the article. H.Y. researched data for the article and contributed to discussion of the content. F.G., J.M., B.A.J., S.S. and A.S. researched data for the article, contributed to discussion of the content and wrote the article. S.U. contributed to discussion of the content and wrote the article. M.S., A.K., A.L.B., H.-U.H. and A.F. contributed to discussion of the content.

Competing interests
Since January 2020, B.A.J. has been an employee and shareholder of Eli Lilly and Company. Outside the current work, R.W. reports lecture fees from Novo Nordisk and Sanofi, and travel grants from Eli Lilly. R.W. served on an advisory board for Akcea Therapeutics and Daiichi Sankyo. In addition to his current work, A.L.B. reports lecture fees from AstraZeneca, Boehringer Ingelheim and Novo Nordisk. A.L.B. served on advisory boards for AstraZeneca, Boehringer Ingelheim and Novo Nordisk. Besides his current work, A.F. reports lecture fees from and advisory board membership for Sanofi, Novo Nordisk, Eli Lilly and AstraZeneca. In addition to his current work, M.H. reports research grants from Boehringer Ingelheim and Sanofi (both to the University Hospital of Tübingen) and lecture fees from Sanofi, Novo Nordisk, Boehringer Ingelheim, Eli Lilly and Merck Sharp & Dohme. He also served on an advisory board for Boehringer Ingelheim. The other authors declare no competing interests.

Peer review information
Nature Reviews Endocrinology thanks A. Gastaldelli and the anonymous reviewer(s) for their contribution to the peer review of this work.

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.