

# Pancreas Volume and Fat Deposition in Diabetes and Normal Physiology: Consideration of the Interplay Between Endocrine and Exocrine Pancreas

Yoshifumi Saisho

Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan  
E-mail: ysaisho@keio.jp

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## ■ Abstract

The pancreas is comprised of exocrine and endocrine components. Despite the fact that they are derived from a common origin *in utero*, these two compartments are often studied individually because of the different roles and functions of the exocrine and endocrine pancreas. Recent studies have shown that not only type 1 diabetes (T1D), but also type 2 diabetes (T2D), is characterized by a deficit in beta-cell mass, suggesting that pathological changes in the pancreas are critical events in the natural history of diabetes. In both patients with T1D and those with T2D, pancreas mass and exocrine function have been reported to be reduced. On the other hand, pancreas volume and pancreatic fat increase with obesity. Increased beta-cell mass with increasing obesity has also been observed in humans, and ectopic fat de-

posits in the pancreas have been reported to cause beta-cell dysfunction. Moreover, neogenesis and transdifferentiation from the exocrine to the endocrine compartment in the postnatal period are regarded as a source of newly formed beta-cells. These findings suggest that there is important interplay between the endocrine and exocrine pancreas throughout life. This review summarizes the current knowledge on physiological and pathological changes in the exocrine and endocrine pancreas (i.e., beta-cell mass), and discusses the potential mechanisms of the interplay between the two compartments in humans to understand the pathophysiology of diabetes better.

**Keywords:** diabetes · endocrine pancreas · exocrine pancreas · interplay · beta-cell mass · pancreatic fat · aging · obesity

## 1. Introduction

The pancreas comprises the exocrine and endocrine compartment, with most of the pancreatic mass included in the former. The exocrine pancreas contains acinar cells that secrete digestive fluid and a duct system through which the fluid drains into the intestine. The endocrine compartment includes the islets of Langerhans, which are scattered throughout the exocrine pancreas, and which comprise only 1-2% of the pancreas. The endocrine pancreas secretes various hormones such as insulin, glucagon, and somatostatin, and plays a key role in glucose metabolism. Because of the different roles and functions

of the endocrine and exocrine pancreas, these two components have usually been studied separately. While diabetes can occur because of pancreatic disease such as pancreatitis or pancreatic cancer [1], recent studies have shown that type 1 diabetes (T1D) and type 2 diabetes (T2D) are characterized by a deficit in beta-cells, an endocrine cell that secretes insulin [2-5], suggesting that pathological changes in the pancreas are critical for the natural history of the disease.

Given that endocrine and exocrine pancreas are derived from the same origin *in utero*, neogenesis and transdifferentiation from the exocrine to the endocrine compartment in the postnatal period have been reported in animal studies [6-10], sug-

gesting that there is continuous interplay between the endocrine and exocrine pancreas throughout life. Therefore, it is important to assess the endocrine and exocrine compartments simultaneously to understand the disease better. This review summarizes recent knowledge regarding physiological and pathological changes in the exocrine and endocrine pancreas in humans, and discusses the interplay between these two compartments of the pancreas.

## 2. Development of exocrine and endocrine pancreas

During human embryonic development, dorsal and ventral pancreatic buds arise from the distal foregut endoderm around 30 days post-conception (embryonic day (e) 9-9.5 in mice); this event coincides with the first detection of a key transcription factor for pancreatogenesis, pancreatic and duodenal homeobox factor 1 (Pdx1) [11, 12]. The ventral bud then rotates around the gut and merges with the dorsal bud into a single organ (e12.5 in mice). Around 50 days post-conception (e15-15.5 in mice), endocrine progenitor cells expressing neurogenin 3 (Ngn3), a transcription factor required for endocrine cell development, are firstly detected in the duct wall (trunk epithelium). Ngn3 upregulation results in separation of endocrine cells from the duct lineage. During this period, the pancreatic epithelium continues to expand and branch into a highly ordered tubular network.

These morphologic changes are paralleled by the differentiation of endocrine, acinar, and ductal cells, all of which are derived from a common origin from progenitor cells in the gut endoderm. Endocrine cells arise from Ngn3-expressing progenitor cells, and the transcription factors Pax4, Pdx1, and Nkx6.1 act as critical beta-cell determinants, whereas Arx determines alpha-cell identity. Endocrine cells become separated from the duct, and cluster to form aggregates, eventually maturing into islets of Langerhans. Beta-cell clusters are well vascularized by 10 weeks post-conception. At 12-13 weeks post-conception, islets containing each type of endocrine cell are apparent. Endocrine cells other than beta- and alpha-cells include delta-cells, pancreatic polypeptide (PP) cells and epsilon-cells, which secrete somatostatin, PP, and ghrelin, respectively. Ngn3 expression is transient, peaking around the end of the first trimester, and is not detected in human fetuses after 35 weeks post-conception. On the other hand, Pdx1 is exclusively expressed by beta-cells in the postnatal period. Finally, beta-cells comprise about 60-80% of endo-

### Abbreviations:

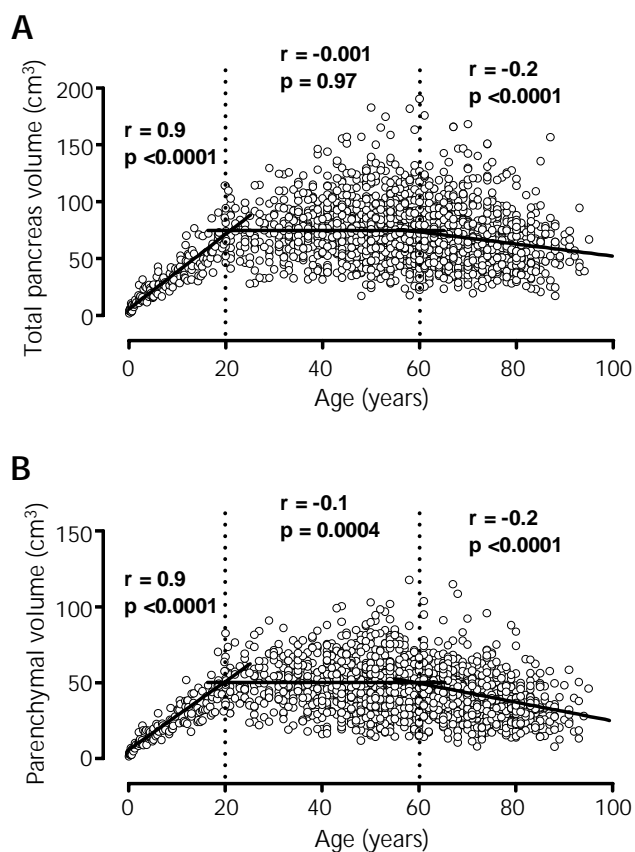
BCM	beta-cell mass
BMI	body mass index
CCK	cholecystokinin
CT	computed tomography
DPP-4	dipeptidyl peptidase-4
DM	diabetes mellitus
ER	endoplasmic reticulum
FDA	Food and Drug Administration
FFA	free fatty acids
F/P	fat/parenchymal
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide 1
GLP-1RA	GLP-1 receptor agonist
HbA1c	glycated hemoglobin
HOMA-IR	homeostasis model assessment of insulin resistance
HOMA- $\beta$	homeostasis model assessment of beta-cell function
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
MRI	magnetic resonance imaging
MRS	magnetic resonance spectrometry
NDM	non-diabetes mellitus
NGT	normal glucose tolerance
OGTT	oral glucose tolerance test
PACAP	pituitary adenylate cyclase activating polypeptide
PDX1	pancreatic and duodenal homeobox factor 1
PET	positron emission tomography
PP	pancreatic polypeptide
T1D	type 1 diabetes
T2D	type 2 diabetes
TNF	tumor necrosis factor

crine cells in each islet, with the exception of the ventral portion of the pancreatic head, in which PP cells are the major component of the endocrine cells [3, 5].

## 3. Physiological and pathological changes in exocrine pancreas mass

### 3.1 Growth in childhood and changes with aging

Pancreas mass is measured anatomically at autopsy or by the use of imaging techniques such as ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI). Of note, pancreas volume measured using CT or MRI is generally smaller (~70 ml) than that measured anatomically (~100 g) [13]. This difference may result from the fact that the pancreas is made up of retroperitoneal tissue surrounded by fat tissue. Thus, resected pancreas contains interlobular fat, resulting



**Figure 1.** Age-related distribution of pancreas volume and fat volume over time. Total (A) and parenchymal (B) pancreas volume from birth to age 100 years measured on the basis of CT scan images ( $n = 1,856$ ) showed a strong correlation between age and total as well as parenchymal pancreas volume from birth to age 20 years ( $y$  (volume;  $\text{cm}^3$ ) =  $5.5 + 3.31x$  (age; years) and  $y = 4.3 + 2.25x$ , respectively). There is a negative correlation between age and total as well as parenchymal volume after age 60 years ( $y = 106.0 - 0.53x$  and  $y = 71.7 - 0.45x$ , respectively). There is no significant correlation between age and total pancreas volume between age 20 and 60 years. Reproduced with permission from the authors of reference [13]

in a greater mass of pancreas compared with that measured by CT or MRI imaging.

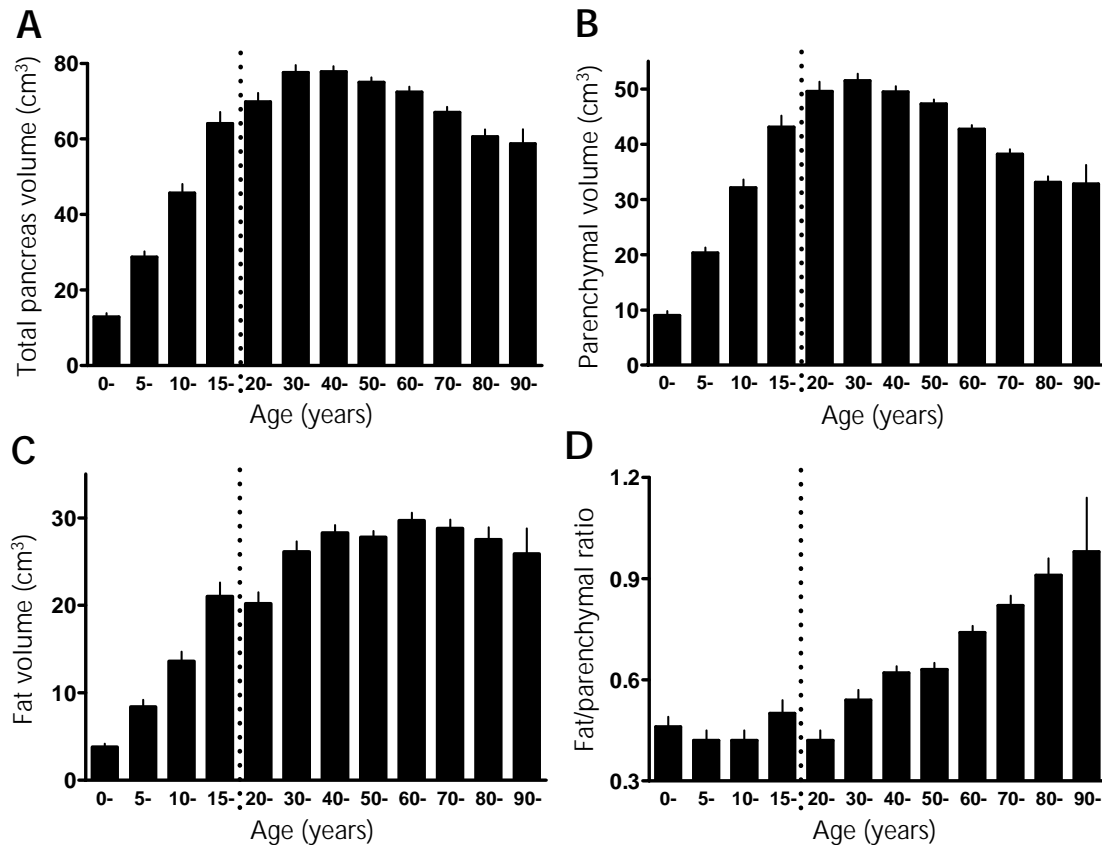
Pancreas mass is approximately 10 g at birth, and then increases linearly with age in childhood and adolescence [13] (**Figure 1**). Pancreas mass reaches a plateau around 20 years of age, at approximately 70 g [13], and then declines in the elderly, from about 60 years of age [13]. The pancreas of older subjects is characterized by atrophy of acinar cells, fibrosis, and fat infiltration in the exocrine pancreas [14]. Thus, parenchymal pancreas

mass estimated by CT density, which presumably consists of acinar and duct compartments, but not fat tissue, declines, and the ratio of fat to parenchymal pancreas increases in the elderly [13] (**Figure 2**). A recent study showed that the ratio of pancreas weight to body weight is constant across a wide range of ages and BMIs [15]. This finding is useful to assess the impact of diabetes on pancreas/beta-cell mass in a mixed population (with varying ages and BMI values) since pancreas mass and volume is reduced in patients with (longstanding and recently diagnosed) T1D compared to that of non-diabetic controls [16, 17]. However, since the portions of parenchyma and fat change with aging and degree of obesity, as described above, pancreas mass and single components of the pancreas should be taken into account when investigating diabetes pathogenesis [18].

### 3.2 Effects of obesity and diabetes on pancreas mass

Pancreas mass increases with obesity [13]. The pancreas of obese subjects is mainly characterized by fat infiltration within exocrine pancreas and interlobular spaces [14]. However, the acinar component also increases with obesity. An analysis of CT images showed that parenchymal pancreas mass increases by about 10-15% in the presence of obesity, whereas pancreatic fat mass increases by ~70%, resulting in ~30% increase in total pancreas mass with obesity [13] (**Figure 3**), which is comparable among different ethnic groups [19, 20].

Pancreas mass is decreased by 30-40% in subjects with T1D [15-17]. Histological analysis showed atrophy of acinar cells in the pancreas [21-23] and impaired exocrine function in patients with T1D [24-26]. Pancreas mass is also decreased in subjects with T2D compared to age- and BMI-matched controls. However, the degree of reduction is smaller (8-20%) than that observed in subjects with T1D [13, 27] (**Table 1**). Impaired exocrine function in patients with T2D has also been reported [25, 26], but to a lesser degree than in patients with T1D, similarly to pancreas mass. Philippe *et al.* reported that pancreas volume is correlated with chymotrypsin activity and stimulated C-peptide level in patients with diabetes, suggesting a close correlation between exocrine and endocrine pancreas [28]. Together, these studies suggest that both T1D and T2D lead to a reduction in pancreas mass and exocrine cell function. The potential mechanisms are discussed in more detail below.



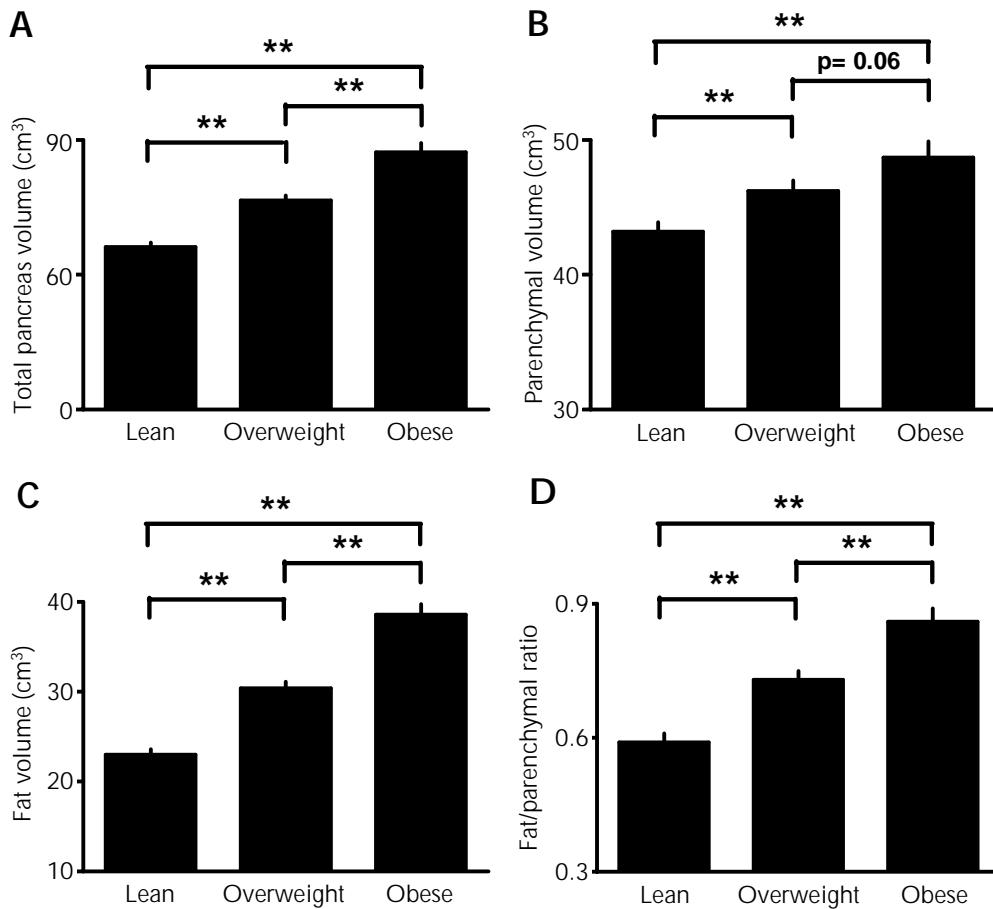
**Figure 2.** Total, parenchymal, and pancreatic fat volumes in each age decile. **A:** total pancreas volume, **B:** parenchymal volume, **C:** fat volume, **D:** fat/parenchyma (F/P) ratio. The total pancreas volume increases with age until ~30 years, and then reaches a plateau. After age 60, total pancreas volume declines due to a decrease in parenchymal pancreas volume. Pancreatic fat remains proportional to pancreas parenchyma volume until the age of ~50 years, after which the F/P ratio increases because of the loss of pancreas parenchyma, while the pancreatic fat amount remains constant. Reproduced with permission from the authors of reference [13].

#### 4. Relationship between pancreas mass and beta-cell mass and their pathophysiological changes

Since it is impossible to measure human beta-cell mass (BCM) *in vivo*, BCM is estimated to be the product of beta-cell area in relation to pancreas area measured by histological analysis (i.e., fractional beta-cell area) and pancreas mass. BCM at birth is approximately 0.1 g, and increases gradually with age in childhood and adolescence [29], reaching a plateau at around the age of 20 at approximately 1 g [14]. In adulthood, BCM remains constant. In the elderly, islet architecture is relatively well preserved and BCM remains stable [14], or is only slightly reduced [3, 30]. This is in contrast to the marked decline in exocrine pan-

creas mass, which is due to acinar atrophy and fibrotic changes. Since insulin sensitivity decreases with aging, the lack of compensatory BCM with aging may result in worsening glucose tolerance in the elderly [31]. However, recent studies have suggested that beta-cell function increases with aging through age-dependent epigenetic modulation [32] or p16<sup>Ink4a</sup>-induced senescence of beta-cells [33], which may contribute to compensatory changes in beta-cell function to preserve normoglycemia with aging. Further studies are needed to clarify the change in “functional” BCM with aging in humans.

In subjects with T1D, most of the beta-cells are destroyed via autoimmune reaction, and BCM eventually decreases to nearly, but usually not absolute, zero [21-23]. Studies have shown that BCM is also decreased in subjects with T2D by 30-60% compared to that in non-diabetic subjects [2-5].



**Figure 3. Effects of obesity on pancreatic volumes.** Total pancreas volume (A), parenchymal volume (B), fat volume (C) and fat/parenchymal (F/P) ratio (D) were measured on the basis of CT scan images in lean ( $n = 230$ ), overweight ( $n = 460$ ), and obese individuals ( $n = 230$ ). All components of the pancreatic volume were significantly increased in overweight and obese subjects compared to lean subjects. \*\*  $p < 0.01$ . Reproduced with permission from the authors of reference [13].

Changes in other endocrine cells are less clear. Both increase and decrease in alpha-cell mass in subjects with T2D have been reported [34-38]. Taken together, these findings indicate that both endocrine and exocrine mass decrease with the natural course of diabetes.

Since BCM is estimated as a product of fractional beta-cell area and pancreas mass, pancreas mass should always be considered when findings of histological analysis are interpreted. For example, fractional beta-cell area has been reported to be decreased by 40-65% in patients with T2D [2]. If pancreas mass were increased, BCM might not be reduced in these patients. However, since pancreas mass is decreased usually in patients with T2D, BCM is confirmed to be decreased to an even greater degree in these patients.

In the presence of obesity, fractional beta-cell area is increased by ~30% [14]. Since pancreatic parenchymal mass is increased by ~15% [13], the estimated BCM is thus assumed to be increased by 50% in the presence of obesity [14]. Of note, we have observed that fractional beta-cell area tends to be increased in older subjects [14]. However, given that pancreatic parenchymal mass is decreased in older subjects, we concluded that net BCM was not increased in these subjects [14]. Thus, understanding the physiological and pathological changes in pancreas mass is important for the determination of BCM.

The change in BCM during the development of T2D remains largely unknown. Obesity is an established risk factor for T2D [39-41]. It results from excess energy intake and physical inactivity,

**Table 1.** Comparison of pancreas volume measured on the basis of CT scan images between humans with type 2 diabetes and age-, sex-, and BMI-matched controls

Variable	Subjects without type 2 diabetes	Subjects with type 2 diabetes
Number (male/female)	660 (304/356)	165 (76/89)
Age (years)	66 ± 12	66 ± 11
BMI (kg/m <sup>2</sup> )	27.6 ± 5.0	27.7 ± 5.6
Pancreas volume (cm <sup>3</sup> )	-	-
Total (cm <sup>3</sup> )	74.9 ± 27.0	70.0 ± 26.5*
Parenchymal volume (cm <sup>3</sup> )	43.1 ± 16.5	39.7 ± 16.4*
Fat volume (cm <sup>3</sup> )	31.7 ± 16.6	30.3 ± 15.2
Fat/parenchymal ratio	0.81 ± 0.50	0.85 ± 0.48

**Legend:** Values are presented as mean ± SD. \* p < 0.05 vs. subjects without type 2 diabetes. *Abbreviations:* BMI - body mass index, CT - computed tomography. Reproduced with permission from the authors of reference [13].

and decreases insulin sensitivity. To maintain normoglycemia, insulin secretion increases with obesity. We and others have shown that, in humans, BCM increases by 20-50% with obesity in the Caucasian population [4, 14], while there is little increase in BCM in the Japanese population [30, 38, 42]. Considering that insulin secretion is increased 2- to 3-fold with obesity [43], the compensatory increase in insulin secretion appears mainly attributable to an increase in insulin secretion per individual beta-cell, resulting in increased workload of beta-cells. Excess beta-cell workload may eventually result in beta-cell damage through various mechanisms such as oxidative stress, endoplasmic reticulum (ER) stress, and amyloid deposition in individuals susceptible to T2D, which may cause beta-cell apoptosis and reduction in BCM even in the absence of hyperglycemia [44]. Indeed, a reduction in BCM in patients with prediabetes has been reported [2, 45, 46], and a significant correlation between glycated hemoglobin (HbA1c) and BCM was observed in both patients with diabetes and those without diabetes [47]. If the reduction in BCM and beta-cell function has started, the “functional BCM” can no longer compensate for insulin resistance, causing hyperglycemia to develop. Hyperglycemia further contributes to beta-cell damage by so-called glucotoxicity, and functional BCM further decreases, contributing to the progressive nature of T2D. An inverse association between BCM and duration of T2D has also been reported, consistent with the progressive loss of beta-cell function during T2D progression [4].

Since both T1D and T2D are characterized by a deficit in beta-cells, fostering beta-cell regeneration is the key to curing both types of diabetes. However, the source of new beta-cells in the postnatal period remains unclear [44, 48]. BCM is

regulated by the balance of newly formed beta-cells and beta-cell loss. Beta-cell replication and neogenesis are considered to be sources of newly formed beta-cells, while beta-cell apoptosis is considered a major cause of beta-cell loss [2, 49]. A recent rodent study has suggested beta-cell dedifferentiation to be another mechanism of beta-cell loss in diabetes [50]. In the postnatal period, beta-cell replication is frequently seen within the first five years of life [29, 51], but it is rarely seen thereafter in humans [14, 38]. Based on the finding that endocrine and exocrine pancreas have a common origin during pancreas development, as described above, the presence of cellular plasticity in the adult pancreas has been suggested and reviewed elsewhere [52]. Cellular plasticity such as beta-cell neogenesis from duct cells or transdifferentiation from acinar cells or other endocrine cells (e.g., alpha-cells) may contribute to newly formed beta-cells, in addition to beta-cell replication. Although the role of beta-cell neogenesis as a source of new beta-cells remains to be established, an increase in insulin-positive duct cells, a surrogate marker for beta-cell neogenesis, has been observed in patients with impaired glucose tolerance [46]. Thus, the exocrine pancreas may have an important role as a source of endocrine cells in beta-cell regeneration.

## 5. Mechanisms of the interplay between endocrine and exocrine pancreas

### 5.1 Effects of islet hormones on exocrine pancreas

Pancreatic parenchymal mass is increased with obesity [13]. Although exocrine mass and function are regulated by numerous factors, studies con-

ducted in the last decades have revealed that islet hormones act as trophic factors in the exocrine pancreas. Insulin is one of the major regulators of exocrine growth and function, impacting the exocrine pancreas locally in a paracrine manner [53]. Thus, reduced pancreas mass in patients with T1D is likely to be mediated by reduced endogenous insulin secretion in these subjects, although a recent study suggested that pancreas volume is already reduced years before the clinical onset of T1D [15, 17]. On the other hand, the increase in pancreas mass with obesity may also be explained by insulin hypersecretion from beta-cells.

The interplay between the endocrine and exocrine pancreas may also be mediated by other islet-derived hormones such as PP and somatostatin, other humoral factors including pancreastatin and ghrelin, and neurotransmitters such as nitric oxide, peptide YY, substance P, pituitary adenylate cyclase activating polypeptide (PACAP), and galanin released by nerves innervating the pancreas, as reviewed elsewhere [54]. Further investigation is needed to clarify the effects of these factors on pancreas mass in humans.

### *5.2 Beta-cell area and function in pancreatic diseases*

Conversely, pathological changes in the exocrine pancreas also affect endocrine pancreas and glucose metabolism. Pancreatic diseases such as pancreatitis and pancreatic cancer often cause hyperglycemia, referred to as pancreatic or pancreatogenic diabetes [55-59]. The mechanisms by which pancreatitis and pancreatic cancer promote hyperglycemia remain to be fully clarified, but insulin secretion is often impaired in these patients [60]. The pancreas of patients with chronic pancreatitis shows atrophic and fibrotic change of the exocrine pancreas [61]. In these patients, although islet architecture is relatively well preserved, fractional beta-cell area is decreased [61]. On the other hand, atrophy of the exocrine pancreas is not obvious in patients with pancreatic cancer, and the effects of pancreatic cancers on islet architecture remain unclear [62, 63].

By examining pancreata from 99 subjects who underwent pancreatic surgery, we found that the fractional beta-cell area in the resected pancreas was significantly decreased in patients with pancreatic cancer compared to that in patients with other pancreatic tumors, and that the reduction was independent of the presence or absence of diabetes [38]. Humoral factors such as amylin and inflammatory cytokines produced by tumors may in-

duce beta-cell dysfunction [59]. Recent studies suggest that adrenomedullin is a mediator of beta-cell dysfunction and impaired glucose metabolism in patients with pancreatic cancer [64].

### *5.3 Obesity-induced inflammation in exocrine pancreas*

Obesity and diabetes are also associated with an increased risk of pancreatitis and pancreatic cancer [65]. While the underlying mechanisms remain unclear, rodent studies have shown that a high-fat diet induces inflammation and fibrosis in the exocrine pancreas [66]. Oxidative stress, impaired autophagy, and ER stress induced by various types of fatty acids have been proposed as mechanisms of inflammation in exocrine tissue [65, 67-69].

While an increase in immune cell infiltration within the exocrine pancreas is a typical event in T1D [70], recent studies have also shown evidence of islet inflammation in patients with T2D [71-76]. A recent rodent study has shown that intestinal bacteria entering the pancreatic duct system could trigger an adverse innate immune response towards beta-cells, leading to the development of T1D [77]. These findings indicate that the interaction between the endocrine and exocrine pancreas may be in part mediated by inflammatory change within the pancreas. It is possible that obesity-induced chronic inflammation in the exocrine pancreas may induce islet inflammation and beta-cell dysfunction, and thus contribute to the changes in pancreas volume observed with obesity and diabetes. Since beta-cell neogenesis from pancreatic ducts and acinar cells has been reported [78], inflammatory changes in the exocrine pancreas may also affect beta-cell neogenesis and influence beta-cell mass.

### *5.4 Anti-diabetic medication and exocrine pancreas*

Recent advances in the development of anti-diabetic agents have provided new therapeutic options for the management of diabetes. Because of the interplay between endocrine and exocrine pancreas, anti-diabetic medication may affect the exocrine pancreas by either changing endocrine function or off-target effects of the agent.

Incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are secreted from the intestine, and enhance insulin secretion in a glucose-dependent manner [79]. In rodents, administration

**Table 2.** Studies reporting an association between pancreatic fat and glucose metabolism

Study	Number	Method	Finding
Saisho et al. (2007) [13]	T2D: 165 NDM: 660	CT	Reduced total and parenchymal pancreas volume, but not pancreatic fat, in T2D
Saisho et al. (2007) [13]	T2D: 23 NDM: 24	Histological examination	No changes in pancreatic fat in T2D
Tushuizen et al. (2007) [123]	T2D: 12 NDM: 24	MRS	Negative association between pancreatic fat and beta-cell function in NDM, but not T2D
Heni et al. (2010) [124]	IFG/IGT: 23 NGT: 28	MRI/MRS	Negative association between pancreatic fat and insulin secretion in IFG/IGT, but not NGT.
van der Zijl et al. (2010) [133]	IFG/IGT: 19 IFG: 29 NGT: 16	MRI/MRS	Pancreatic fat increased with progression of abnormal glucose tolerance (NGT<IFG<IFG/IGT). Negative association between pancreatic fat and disposition index, but not insulin secretion.
Lim et al. (2011) [127]	T2D: 11 NDM: 8	MRI	Dietary energy restriction for 8 weeks decreased pancreatic fat and improved beta-cell function
Szczepaniak et al. (2012) [126]	NDM: 100	MRS	Positive association between pancreatic fat and insulin secretion in black and white, but not Hispanic, subjects
Yokota et al. (2012) [125]	DM: 62 IGT: 52 NGT: 53	CT	Negative association between pancreatic fat and insulin secretion
Ou et al. (2013) [119]	DM: 483 Pre-DM: 1,225 NGT: 5,446	Sonography	Association between fatty pancreas and DM
Wang et al. (2014) [115]	FP: 1,297 Non-FP: 6,800	Sonography	Association between fatty pancreas and DM in male, but not female, subjects
Lim et al. (2014) [116]	T2D: 156 NDM: 50	CT	Reduced pancreas volume and increased pancreatic fat in T2D. Positive association between pancreatic fat and HOMA-IR.
Gaborit et al. (2014) [120]	Obese T2D: 19 Obese NDM: 13 Healthy control: 13	MRS	Increased pancreatic fat in T2D
Wong et al. (2014) [134]	PF >10.4%: 110 PF ≤10.4%: 575	MRI/MRS	Association between pancreatic fat and HOMA-IR, but not HOMA-β.
Kim et al. (2014) [117]	IFG/IGT/DM: 29 NGT: 33	CT	Association between pancreatic fat and IFG/IGT/DM
Honka et al. (2014) [128]	Obese DM: 20 Obese NDM: 32 Healthy control: 25	PET	Negative association between pancreatic fat and beta-cell function
Kühn et al. (2015) [136]	T2D: 70 Pre-DM: 431 NGT: 740	MRI	No association between pancreatic fat and DM
Honka et al. (2015) [129]	Obese DM: 10 Obese NDM: 13 Healthy control: 15	PET	Association between loss of pancreatic fat and improvement in beta-cell function after bariatric surgery
Begovatz et al. (2015) [137]	T2D: 14 IFG/IGT: 14 NGT: 28	MRI/MRS	No association between pancreatic fat and beta-cell dysfunction
Macauley et al. (2015) [118]	T2D: 41 NDM: 14	MRI	Reduced pancreas volume and increased pancreatic fat in T2D. Association between pancreas volume, but not pancreatic fat, and HOMA-β.
Steven et al. (2016) [122]	T2D: 18 NDM: 9	MRI	Increased pancreatic fat in T2D

**Legend:** CT – computed tomography, DM – diabetes mellitus, FP – fatty pancreas, IFG – impaired fasting glucose, IGT – impaired glucose tolerance, MRI – magnetic resonance imaging, MRS – magnetic resonance spectroscopy, NDM – non-diabetes mellitus, NGT – normal glucose tolerance, HOMA-IR – homeostasis model assessment of insulin resistance, HOMA-β – homeostatis model assessment of beta-cell function, PET – positron emission tomography, T2D – type 2 diabetes.



of GLP-1 or GIP promotes beta-cell proliferation and increase in BCM [80]. Incretin-based medicine, including dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 receptor agonists (GLP-1RAs), is now widely used for the treatment of T2D. DPP-4 inhibitors prevent the degradation of incretin through DPP-4 inhibition, thereby enhancing endogenous incretin action. GLP-1RAs are injectable drugs that activate the GLP-1 receptor at a supra-physiological level. Incretin-based medicine is associated with a low risk of hypoglycemia and a favorable weight profile in addition to its glucose-lowering effect [79].

However, since the start of incretin-based medicine several case reports on the development of acute pancreatitis have been published, and the US Food and Drug Administration (FDA) has issued a “black box warning” for these drugs [81]. Incretin-induced pancreatitis and subsequent oncogenesis have been suggested by some animal studies [82-85], but the results are conflicting [86-90]. It has also been shown that the GLP-1 receptor is expressed in some but not all pancreatic exocrine cells [91], while DPP-4 is expressed in some (~30%) duct cells [92]. To date, no significant association between incretin therapy and pancreatitis or pancreatic cancer has been confirmed in either large-scale cohort studies or randomized controlled trials [93-95].

Using autopsy pancreas, Butler *et al.* reported that pancreas mass was increased by ~40% in subjects with T2D who had been treated with incretin-based medicine [96], although these results may have been confounded by other factors [97, 98]. A recent rodent study showed that incretin therapy increases pancreas mass by ~30% as a result of enhanced protein synthesis [99]. Although we have reported that there was no change in pancreas volume measured by CT scan 6 months after the initiation of liraglutide treatment [100], a slight increase in amylase or lipase after treatment with GLP-1RA has been consistently observed [100-103]. The mechanisms by which incretin therapy increases pancreatic enzyme levels remain unclear. Further studies are needed to clarify the effect of incretin-based therapy on pancreas mass.

## 6. Components of the pancreas: role of pancreatic fat deposition

### 6.1 Ectopic fat deposition and diabetes: the lipotoxicity hypothesis

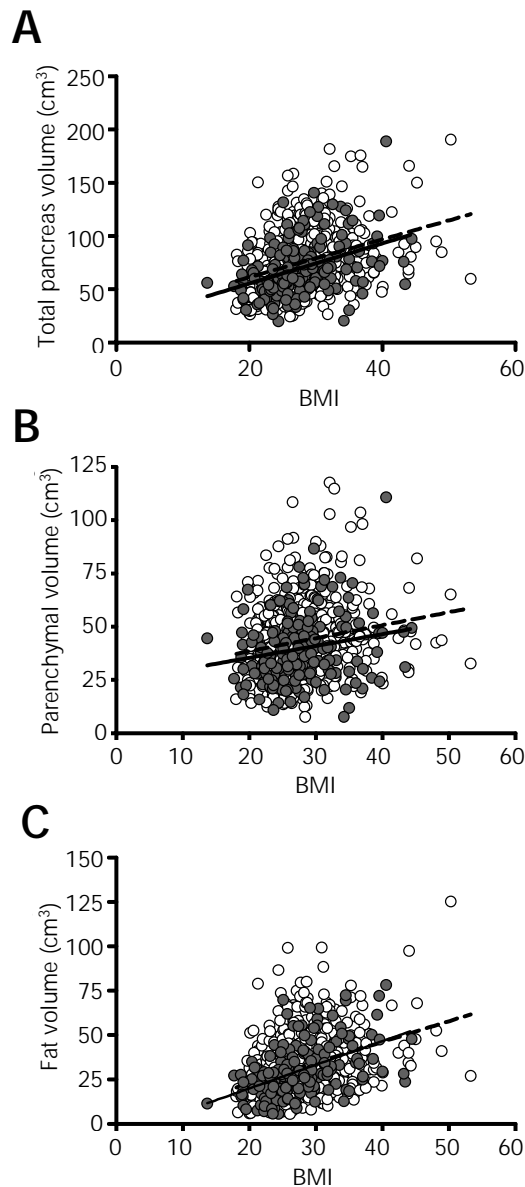
Obesity, especially visceral adiposity, is associated with the development of T2D [104]. The com-

ination of excessive caloric intake and minimal physical activity results in increased fat storage. When fat supply exceeds the capacity of subcutaneous fat storage, spillover of fat leads to ectopic fat deposits in various tissues such as visceral tissue, liver, heart, and skeletal muscle. Ectopic fat deposition also occurs in the pancreas [105-108], which is known as pancreatic steatosis [109].

The association of ectopic fat deposition in various tissues with tissue dysfunction and metabolic derangements is known as the lipotoxicity hypothesis [110-112]. Therefore, fat deposits in the pancreas are an area of active investigation, besides pancreas mass. Pancreatic fat content is increased with obesity, and intra- and interlobular adipocytes, acinar cell fat content, and islet fat content appear to increase proportionally with obesity [105, 108]. Lee *et al.* reported that the accumulation of fat in islets causes beta-cell dysfunction and diabetes in rodents [113]. It has also been shown that the incubation of beta-cells with free fatty acids impairs insulin secretion and promotes beta-cell apoptosis [114]. Furthermore, leptin, tumor necrosis factor (TNF)-alpha, and other adipocytokines secreted from adipocytes within the pancreas may induce beta-cell damage in a paracrine manner. These findings point to a deleterious impact of lipotoxicity on beta-cells, which needs to be clarified *in vivo* in more detail. Currently, the association between fat accumulation in the pancreas and glucose metabolism is an area of ongoing investigation.

### 6.2 Pancreatic fat, beta-cell function, and glucose intolerance

It has been reported that pancreatic fat quantified by either sonography, CT, MRI, or MR spectroscopy (MRS) is increased in patients with dysglycemia [115-122], and pancreatic fat content is negatively correlated with beta-cell function [123-127] (**Table 2**). Honka *et al.* have recently studied pancreatic metabolism and blood flow in obese subjects, using positron emission tomography (PET) [128]. The obese individuals showed increased pancreatic fatty acid uptake and fat accumulation and reduced pancreatic blood flow; both of these effects were inversely associated with beta-cell function [128]. The same group also reported improvement in these factors and beta-cell function in patients with T2D who had received bariatric surgery [129]. Thus, not only pancreatic fat, but also pancreatic blood flow, may be associated with impaired beta-cell function in obese subjects.



**Figure 4. Relationship between BMI and pancreatic volume measured on the basis of CT scan images.** Despite considerable individual variance, there is a significant relationship between BMI and total (A), parenchymal (B), and fat (C) volumes in non-diabetic subjects (white dots, broken line) and subjects with type 2 diabetes (T2D) (gray dots, solid line). The relationships are comparable in individuals with T2D and non-diabetics (NDM). **A:** NDM,  $r = 0.3$ ,  $p < 0.0001$ ; T2D,  $r = 0.4$ ,  $p < 0.0001$ . **B:** NDM,  $r = 0.2$ ,  $p < 0.0001$ ; T2D,  $r = 0.2$ ,  $p = 0.01$ . **C:** NDM,  $r = 0.4$ ,  $p < 0.0001$ ; T2D,  $r = 0.5$ ,  $p < 0.0001$ . Reproduced with permission from the authors of reference [13].

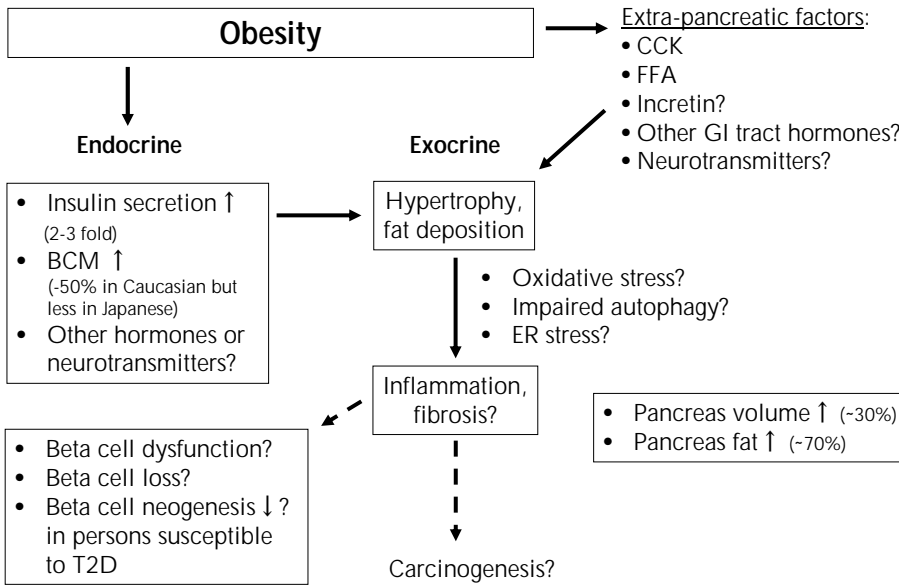
However, inconsistent results have been obtained regarding the association between pancre-

atic fat and glucose metabolism in humans. Pancreatic fat is characterized by adipocyte infiltration in the interlobular and intralobular pancreas [14, 105, 109]. Since a major part of the pancreatic fat is due to adipocyte infiltration, fat distribution in the pancreas is often heterogeneous, which complicates the determination of fat content and distribution in the pancreas, and which may provide a reason for the inconsistencies.

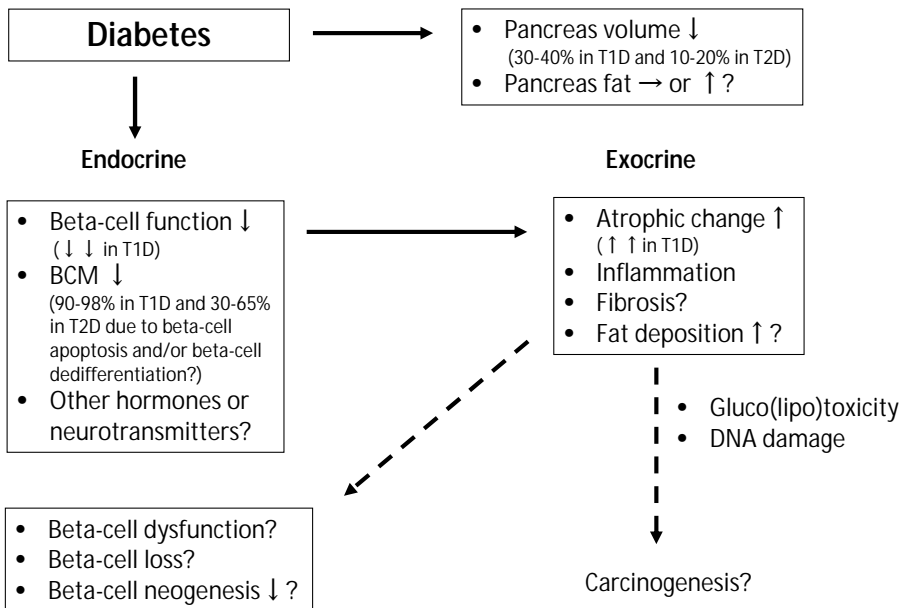
It has also been reported that fat deposits are larger in the body and tail than in the head of the pancreas [130]. However, since pancreatic fat content may also be affected by age and obesity, a causal association between pancreatic fat content and glucose intolerance or beta-cell dysfunction is difficult to establish [106, 131-136]. In our analysis, using CT scan, there was a significant correlation between pancreatic fat content and BMI, but no significant difference in pancreatic fat volume between subjects with and without T2D who were matched for age, sex, and BMI [13] (Table 1 and Figure 4). Histological analysis also showed no significant difference in intralobular pancreatic fat area between age- and BMI-matched subjects with and without T2D [13]. In a recent study, pancreatic intralobular fat was measured carefully by using MRI/MRS techniques and excluding interlobular and peripancreatic fat. There was no association between total or intralobular pancreatic fat and beta-cell function, fasting glucose level, or 2-h glucose level during a 75-g oral glucose tolerance test (OGTT) in patients with and without dysglycemia, while total and intralobular pancreatic fat was positively correlated with age [137]. Consequently, although pancreatic fat has been postulated as a potential cause of beta-cell damage, a causal association between pancreatic fat, beta-cell dysfunction, and glucose intolerance in humans remains to be established. Further investigation is warranted.

## 7. Conclusions

This review has summarized the physiological and pathological changes in exocrine pancreas and beta-cell mass in response to fat accumulation in the pancreas, and has discussed potential biological mechanisms. The changes in pancreas volume and fat deposition in diabetes as opposed to normal physiology, and the potential mechanisms of the interplay between the endocrine and exocrine pancreas are summarized in Figures 5-7. Since these two compartments of the pancreas arise from the same origin, changes in one compartment are considered to affect the other.



**Figure 5. Pathophysiological changes in pancreas volume in the presence of obesity and potential mechanisms of the interplay between endocrine and exocrine pancreas.** Pancreas volume increases with obesity. Insulin acts as a trophic factor on the exocrine pancreas. Inflammatory changes in the exocrine pancreas may affect endocrine function and/or mass. *Abbreviations:* BCM – beta-cell mass, CCK – cholecystokinin, ER – endoplasmic reticulum, FFA – free fatty acid, GI – gastrointestinal, T2D – type 2 diabetes.



**Figure 6. Pathophysiological changes in pancreas volume in the presence of diabetes and potential mechanisms of the interplay between endocrine and exocrine pancreas.** Pancreas volume decreases in the presence of diabetes. Insulin acts as a trophic factor on the exocrine pancreas. Inflammatory changes in the exocrine pancreas may affect endocrine function and/or mass. *Abbreviations:* BCM – beta-cell mass, DNA – deoxyribonucleic acid, T1D – type 1 diabetes, T2D – type 2 diabetes.

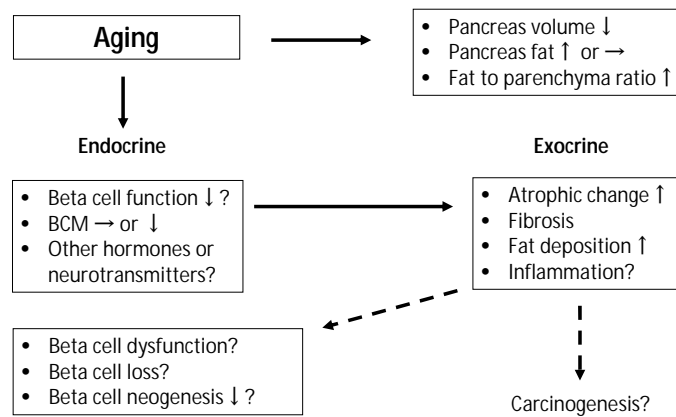
It is well known that there are several causes of reduced endocrine pancreatic function, including aging, obesity, and diabetes. However, it remains largely unclear how beta-cell mass and function are affected exactly by these factors. Pancreas volume, pancreatic fat content, and beta-cell mass change with aging, with fat content being increased and beta-cell mass reduced. The harmful effect of increased pancreatic fat content may be caused by acinar atrophy and fibrosis in the exocrine pancreas, which may negatively affect endocrine cell function and cell formation. As mentioned above, obesity is another cause of declined beta-cell mass and impaired function. The reason is that pancreatic fat content can be increased in obesity, suggesting that pancreatic fat deposits have a deleterious effect on beta-cell mass and function. However, this hypothesis also remains controversial, and needs to be verified by further studies.

In contrast, the effects of diabetes on beta-cell mass and function are largely common; both T1D and T2D are characterized by a deficit in beta-cell mass. Therefore, prevention or reversal of beta-cell loss could be possible therapies for both types of diabetes. In this regard, a better understanding of the interplay between exocrine and endocrine pancreas may help to clarify the

mechanisms regulating the pancreatic components, and eventually to cure diabetes through beta-cell preservation or even regeneration.

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**Figure 7.** Pathophysiological changes in pancreas volume in the presence of aging and potential mechanisms of the interplay between endocrine and exocrine pancreas. Pancreas volume decreases in the presence of aging and beta-cell function reduces. Abbreviation: BCM – beta-cell mass.

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