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REVIEW

Intra-Pancreatic Fat Deposition and Pancreatitis: Insights from the COSMOS Program

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Abstract: The global burden of pancreatitis is substantial, bedevilled by the lack of pathogenesis-based treatments for acute pancreatitis and chronic pancreatitis. The integrated PANDORA (PANcreatic Diseases Originating from intRa-pancreatic fAt) hypothesis "moved the needle" on thinking why pancreatitis develops by bringing fat in the pancreas to the fore. A total of 20 original clinical studies exploring an uncharted territory of fat in the pancreas and pancreatitis were published between 2019 and 2024 as part of the COSMOS (Clinical and epidemiOlogical inveStigations in Metabolism, nutritiOn, and pancreatic diseaseS) program. This review concisely summarises the novel insights into the relationship of intra-pancreatic fat deposition with endocrine and exocrine pancreatic functions, behavioural and nutritional factors, as well as various biomarkers. Tapping into the wealth of knowledge derived from the COSMOS program can unlock new perspectives on the treatment of acute pancreatitis and chronic pancreatitis.

Keywords: intra-pancreatic fat deposition, acute pancreatitis, chronic pancreatitis

Introduction

Excess adiposity is widely acknowledged as a major public health concern.[1,2] While general adiposity is commonly quantified in clinical and epidemiological settings using body mass index, the body mass index-based classification of obesity is relatively insensitive and has led to underestimation of the true burden of excess adiposity.[3] There has been increasing shift from using body mass index to body fat distribution as a more precise harbinger of various pathologies. With the advancement of modern imaging techniques, such as magnetic resonance imaging (MRI), it is now fairly straightforward to non-invasively assess body composition and accurately quantify ectopic fat depots.[4–6] One of the most worrisome depots is intra-pancreatic fat deposition (IPFD) – the lipids scattered within the pancreas (but not peri-pancreatic fat).

The pancreas is a key metabolic organ and a major regulator of body metabolism. Endocrine pancreatic function is central to glucose homeostasis through secretion of insulin, glucagon, and other hormones, whereas exocrine pancreatic function is crucial to digestive physiology through enzymatic lipid, carbohydrate, and protein metabolism.[7,8] Accumulating evidence supports the deleterious effects of excess adiposity on functions of the pancreas, as well as their implications for diseases of the pancreas.[9–11] The PANDORA (PANcreatic Diseases Originating from intRa-pancreatic fAt) hypothesis postulates that high IPFD is a shared driver of all the main sporadic diseases of the pancreas, including both diseases of the endocrine pancreas (eg, type 2 diabetes mellitus) and diseases of the exocrine pancreas (eg, acute pancreatitis, chronic pancreatitis).[12] In particular, the third and fourth predictions of the PANDORA hypothesis are specifically related to high IPFD heightening the risks of developing acute pancreatitis and chronic pancreatitis. An aberrant intra-acinar crosstalk between IPFD (more specifically, lipid droplets) and the endoplasmic reticulum, which may not necessarily involve activation of proteolytic enzymes, plays a major role in the acinar cell injury that initiates acute pancreatitis. When it comes to chronic pancreatitis, the lipotoxicity that emanates from high IPFD leads to activation of anti-inflammatory mechanisms in the pancreas, one manifestation of which is pancreatic fibrosis.[12] COSMOS (Clinical and epidemiOlogical inveStigations in Metabolism, nutritiOn, and pancreatic diseaseS) was launched in 2015 as the world-first purposely designed research program primarily aiming to conduct original prospective research on metabolic derangements in diseases of the pancreas.[13–15] The insights from this program related to IPFD and pancreatitis form the basis of the present review.

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Methodology

Program Participants

Adults (aged 18 or above) who resided in Auckland were eligible if they had a primary diagnosis of acute pancreatitis or chronic pancreatitis established based on international guidelines. The diagnosis of acute pancreatitis required the presence of two of the following criteria: elevation of serum levels of lipase or amylase at least 3-times above the upper limit of normal, upper abdominal pain, and imaging evidence of AP during hospitalisation.[16] The diagnosis of chronic pancreatitis was established if the Cambridge grade was 3 or above and/or parenchymal or ductal calcifications were detected on cross-sectional imaging.[17] The exclusion criteria were as follows: congenital anomalies of the pancreas, pancreatic lipomatosis or lipomatous pseudohypertrophy, hereditary pancreatitis, cystic fibrosis, pancreatic cancer or premalignant lesions, any other malignancy, post-endoscopic retrograde cholangiopancreatography pancreatitis, pancreatic trauma, interventions involving the pancreas (including surgical, endoscopic, or radiologic), steroid therapy, autoimmune pancreatitis, metallic foreign body implants, heart pacemakers, or other implantable electronic devices, or pregnancy. Also, individuals with a confirmed attack of pancreatitis within 3 months prior to enrolment were excluded.[18–22] In addition, healthy adults were recruited. They had no personal or family history of diseases of the exocrine pancreas, diabetes, malignancy, cystic fibrosis, symptoms of upper abdominal pain and nausea, celiac disease, no history of acute infectious or inflammatory conditions requiring medical evaluation or treatment in the 6 months prior to recruitment. Informed consent was obtained from all study participants.

Body Composition Measurements

Participants underwent MRI at the Centre for Advanced Magnetic Resonance Imaging. A 3.0 Tesla MAGNETOM scanner (Siemens, Erlangen, Germany) was used to acquire abdominal images using the same protocol (involved participants lying in the supine position while holding their breath for 11s at end-expiration) for all individuals. Axial T1-weighted volumetric interpolated breath-hold examination Dixon sequence was applied. The following parameters were used: TE, 2.46 ms, 3.69 ms; TR, 5.82 ms; flip angle, 9°; pixel bandwidth, 750 Hz; true form abdomen shim mode; signal average, 1; FOV, 440 mm; base resolution, 512; slice thickness, 5 mm, with a field of view of 500×400 mm, matrix 512 × 410, using partial Fourier and parallel imaging with a total acceleration factor of 2.8. Four types of images were generated – fat-only, water-only in-phase, and out-of-phase images (exported as DICOM files). Two raters (blinded to participant characteristics) measured IPFD, total pancreas volume and diameters, skeletal muscle fat, subcutaneous fat, and visceral fat, TPV, and pancreas diameters in duplicate (Figure 1). Two independent measurements were averaged. An intra-class correlation coefficient was calculated to assess the inter-rater reliability and was deemed to be excellent (intra-class correlation coefficient of more than 0.9) for all the above measurements.[23]

IPFD was determined using a modified "MR-opsy" technique.[24] The pancreas outline was traced on each slice in which it was visible and water-only images served as the reference for each slice.[25,26] Two candidate slices with clear visualisation of the pancreas were selected from a series of abdominal scans. Three regions of interest were placed in the head, body, and tail region of the pancreas to estimate IPFD. A thresholding range of 1–20% was applied to prevent the inclusion of non-parenchymal tissues (such as visceral fat, the main pancreatic duct, blood vessels) within the selected regions of interest. IPFD was calculated as the average pancreatic fat fraction (%) of the two slices.[24] Total pancreas volume, measured in cubic centimetres, was obtained by multiplying the pixel content from all the slices in series with the pixel area and slice thickness.[27–29] The total muscle area and skeletal muscle fat area of the erector spinae muscles were measured using a single axial slice at the lower endplate of L3 vertebra.[30,31] Visceral fat volume and subcutaneous fat volume were quantified manually at L2 – L5. Hepatic fat was determined with the use of magnetic resonance spectroscopy by a single rater. A single voxel (20 × 20×20 mm) was placed in the right lobe of the liver, away from the blood vessels and bile ducts and at least 10 mm away from the organ's edge.[32]

Other Measurements

Venous blood samples were collected on the day of MRI (after 8 to 10 h of fasting) in an ethylene-diamine-tetra-acetic acid tube and lithium heparin tube. Fresh blood samples were sent to a tertiary referral medical laboratory, which measured glycated haemoglobin, plasma glucose, insulin, and lipid panel (HDL cholesterol, LDL cholesterol, total cholesterol,

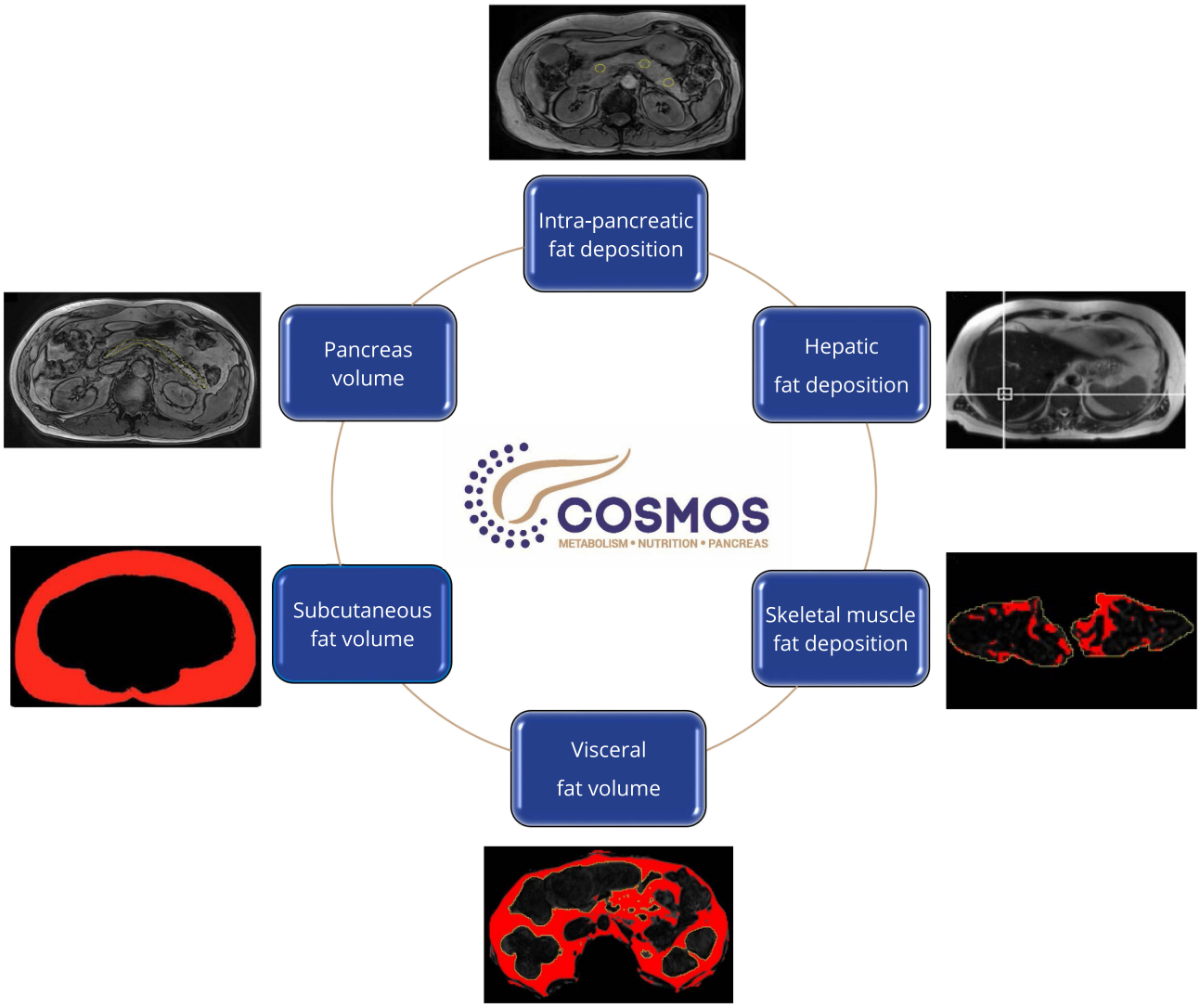

Figure 1 Comprehensive body phenotyping in the COSMOS program.

triglycerides). The remaining blood samples were centrifuged, the plasma was separated into aliquots and stored at −80 °C until use.

Habitual dietary intake over a 12-month period prior to MRI was determined with the use of the EPIC-Norfolk food frequency questionnaire.[33] This tool enabled collection of frequency and portion sizes of 131 food items, which were coded and processed using the FETA software – an open-source, cross-platform tool designed to process dietary data from the food frequency questionnaires in line with the guidelines.[34–37] Data on behavioural factors were collected using a standardised questionnaire at the time of MRI.[38]

Key Findings

A total of 20 original COSMOS studies investigated IPFD in the context of pancreatitis.[39–58] Table 1 presents characteristics of the individual studies.

IPFD and Endocrine Pancreatic Function

The differences in distribution of ectopic fat were investigated between individuals after acute pancreatitis (with and without diabetes mellitus) and healthy controls.[40] Individuals in the diabetes group had significantly higher IPFD than

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Table 1 COSMOS Studies Investigating IPFD in the Context of Pancreatitis

Study ID	Year of Publication	Main Aspect Investigated	Number of Participants*	Study Design	Covariates Accounted for Statistically	Reference
#1	2019	IPFD and endocrine pancreatic function	34	Cross-sectional	According to stepwise regression	[39]
#2	2019	IPFD and endocrine pancreatic function	84	Cross-sectional	Age, sex	[40]
#3	2019	Biomarkers of IPFD	90	Cross-sectional	Age, sex, visceral-to-subcutaneous fat volume ratio, glycated haemoglobin, APACHE II score, time since AP, aetiology of AP, recurrence of AP	[41]
#4	2019	Biomarkers of IPFD	79	Cross-sectional	Age, sex, ethnicity, visceral-to-subcutaneous fat volume ratio, Charlson comorbidity index, glycated haemoglobin, homeostasis model assessment of insulin resistance, time since AP, aetiology of AP, recurrence of AP	[42]
#5	2019	Biomarkers of IPFD	90	Cross-sectional	Age, sex, visceral-to-subcutaneous fat volume ratio, use of lipid-lowering drugs, glycated haemoglobin, APACHE II score, time since AP, aetiology of AP, recurrence of AP	[43]
#6	2020	IPFD and behavioural factors	120	Cross-sectional	Age, sex, ethnicity, glycated haemoglobin, physical activity, tobacco smoking, alcohol consumption	[44]
#7	2020	IPFD and behavioural factors	119	Cross-sectional	Age, sex, ethnicity, visceral-to-subcutaneous fat volume ratio, glycated haemoglobin, triglycerides	[45]
#8	2020	Biomarkers of IPFD	84	Cross-sectional	Age, sex, body mass index, glycated haemoglobin, tobacco smoking, alcohol consumption, triglycerides	[46]
#9	2020	IPFD and endocrine pancreatic function	46	Cross-sectional	Age, sex, glycated haemoglobin	[47]
#10	2021	IPFD and nutrition	111	Cross-sectional	Age, sex, body mass index, use of antidiabetic medications, daily energy intake, recurrence of AP	[48]
#11	2021	IPFD and nutrition	18	Randomised controlled trial	Nil	[49]
#12	2021	IPFD and exocrine pancreatic function	60	Case-control	Age, sex, body mass index, glycated haemoglobin, use of antidiabetic medications, triglycerides, tobacco smoking, alcohol consumption	[50]

(*Continued*)

Table 1 (Continued).

Study ID	Year of Publication	Main Aspect Investigated	Number of Participants*	Study Design	Covariates Accounted for Statistically	Reference
#13	2021	IPFD and nutrition	111	Cross-sectional	Age, sex, body mass index, use of antidiabetic medications, daily energy intake, recurrence of AP	[51]
#14	2022	Biomarkers of IPFD	94	Cross-sectional	Age, sex, visceral-to-subcutaneous fat volume ratio, glycated haemoglobin, APACHE II score, time since AP, aetiology of AP, recurrence of AP	[52]
#15	2022	IPFD and exocrine pancreatic function	108	Cross-sectional	Age, sex, body mass index, fasting plasma glucose	[53]
#16	2022	IPFD and pancreatitis	50	Case-control	Age, sex, body mass index, fasting plasma glucose, triglycerides, aetiology of AP	[54]
#17	2022	Biomarkers of IPFD	105	Cross-sectional	According to stepwise regression	[55]
#18	2023	IPFD and pancreatitis	137	Cross-sectional	Age, sex, ethnicity, body mass index, glycated haemoglobin, triglycerides	[56]
#19	2023	Biomarkers of IPFD	76	Cross-sectional	Age, sex, ethnicity, body mass index, glycated haemoglobin, triglycerides	[57]
#20	2024	Biomarkers of IPFD	116	Cross-sectional	Age, sex, body mass index, glycated haemoglobin	[58]

Notes: *Only participants with a history of pancreatitis. Studies are numbered in the order of their indexation in PubMed.
Abbreviations: AP, acute pancreatitis; APACHE, acute physiology and chronic health evaluation.

individuals without diabetes and healthy controls. There was no significant difference between the groups in terms of hepatic fat.[40]

The associations of a comprehensive panel of insulin traits and glucoregulatory hormones with IPFD were investigated in individuals with new-onset prediabetes or diabetes after acute pancreatitis.[39] Fasting insulin, HOMA-IR, and Raynaud index were significantly associated with IPFD in linear regression analysis. Of them, Raynaud index contributed the most (20%) to variance in IPFD in these individuals. Other studied insulin traits (HOMA-β, insulinogenic index 30', insulinogenic index 60', C-peptide, Stumvoll index, adipose tissue insulin resistance) were not significantly associated with IPFD. None of the studied glucoregulatory hormones and related peptides (gastric inhibitory polypeptide, glucagon-like peptide 1, dipeptidyl peptidase 4, oxyntomodulin) was associated with IPFD.[39]

The associations of indices of insulin sensitivity with IPFD were investigated in non-obese individuals with new-onset prediabetes or diabetes after acute pancreatitis, individuals with type 2 diabetes or prediabetes, and healthy controls.[47] Both fasting state (Raynaud index, HOMA-IR, triglyceride and glucose index) and postprandial state (Matsuda index) indices of insulin sensitivity were significantly associated with IPFD in participants with new-onset prediabetes or diabetes after acute pancreatitis. These findings were independent of age, sex, and glycated haemoglobin. The same associations were not statistically significant in individuals with type 2 diabetes or prediabetes and healthy individuals.[47]

PFD and Exocrine Pancreatic Function

The associations of pancreas size (pancreas volume and diameters of the head, body, and tail of the pancreas) and circulating levels of pancreatic enzymes (pancreatic amylase, pancreatic lipase, and chymotrypsin) with IPFD were investigated in individuals after acute pancreatitis.[53] IPFD was significantly negatively associated with diameter of the tail of the pancreas (but neither total pancreas volume nor diameters of the head and body of the pancreas). Circulating

levels of pancreatic amylase were significantly positively associated with diameter of the tail of the pancreas (but not total pancreas volume or diameters of the head and body of the pancreas) in individuals after acute pancreatitis. These were independent of body mass index, age, sex, and fasting plasma glucose. Levels of pancreatic amylase, pancreatic lipase, and chymotrypsin were not significantly associated with IPFD.[53]

The associations between circulating levels of pancreatic enzymes (pancreatic amylase, pancreatic lipase, and chymotrypsin) and IPFD were investigated in individuals with new-onset prediabetes or diabetes after acute pancreatitis, individuals with type 2 diabetes or prediabetes, and healthy controls.[50] Circulating levels of pancreatic amylase were significantly associated with IPFD in individuals with new-onset prediabetes or diabetes after acute pancreatitis. By contrast, this association was not statistically significant in the other two groups. Circulating levels of pancreatic lipase and chymotrypsin were not significantly associated with IPFD in any group. In individuals with new-onset prediabetes or diabetes after acute pancreatitis, IPFD contributed 15% to variance in pancreatic amylase, 3% - pancreatic lipase, and 1% - chymotrypsin. This was compared with hepatic fat, which contributed 3% to variance in pancreatic amylase, 1% - pancreatic lipase, and 6% - chymotrypsin.[50]

IPFD and Pancreatitis

One study investigated IPFD as a harbinger of acute pancreatitis.[54] A 1% increase in IPFD (but not hepatic fat deposition or skeletal muscle fat deposition) was significantly associated with a more than 30% higher chance of developing the first attack of acute pancreatitis. Further, a 1% increase in IPFD (but not hepatic fat deposition or skeletal muscle fat deposition) was significantly associated with a 67% higher chance of developing the first attack of acute pancreatitis in individuals with normotriglyceridaemia. By contrast, the same associations were not significant in individuals with hypertriglyceridaemia. Notably, these associations were independent of age, sex, body mass index, and fasting plasma glucose.[54] IPFD was also compared between individuals with acute pancreatitis and individuals with chronic pancreatitis.[56] The two groups did not differ significantly in terms of IPFD. This held true in both unadjusted analysis and after accounting for sex, age, body mass index, ethnicity, glycated haemoglobin, and triglycerides.[56]

IPFD and Behavioural Factors

The associations of tobacco smoking, alcohol consumption, and cannabis use with IPFD were investigated in individuals after acute pancreatitis or chronic pancreatitis.[44,45] Tobacco smoking contributed 6.5% to variance in IPFD in these individuals, as compared with 0.6% contribution to variance in hepatic fat and 0.4% contribution to variance in skeletal muscle fat.[45] The amount of variance explained by alcohol consumption was also higher for IPFD (2.8%) than the other ectopic fat depots (1.1% and 2.5% for hepatic and skeletal muscle fat, respectively). Notable was the comparatively lower contribution of alcohol consumption than tobacco smoking to variance in IPFD (2.8% versus 6.5%) in the same individuals with a history of pancreatitis. It was also found that the quantity of tobacco smoked (defined by packs/day) contributed to a greater variance in IPFD than the duration of smoking (defined by number of years smoking). At the same time, the duration of alcohol consumption (defined by number of years drinking) was a greater contributor to IPFD variance than the quantity of consumed alcohol (defined by units/day).[45] In the analysis of cannabis use, regular cannabis users had similar IPFD compared with never users.[44] By contrast, regular cannabis users had significantly higher hepatic fat than never users. Also, cannabis use explained 9.2% of variance in hepatic fat but only 0.2%variance in IPFD.[44]

IPFD and Nutrition

The associations between habitual dietary carbohydrate intake and insulin traits were investigated in individuals after acute pancreatitis and healthy controls, taking into account IPFD.[48] Starch intake was significantly negatively associated with fasting insulin, HOMA-IR, and HOMA-β in the high IPFD group. This was independent of sex, age, body mass index, use of anti-diabetic medications, daily energy intake, and recurrence of acute pancreatitis. Total sugar intake was significantly positively associated with fasting insulin and HOMA-β (taking into account the above-mentioned covariates), but not associated with HOMA-IR. None of the above associations was statistically significant in the other study groups (low IPFD, moderate IPFD, healthy controls). The studied associations differed significantly between the high IPFD group (but not the low IPFD or moderate IPFD groups) and the healthy controls group, which suggests a modifying

effect of IPFD on the associations of habitual intake of total sugar and starch with insulin traits. Intake of non-starch polysaccharides did not have a consistent pattern of associations with insulin traits.[48]

In a similar fashion, a modifying effect of IPFD on the associations between habitual dietary fat intake and insulin traits was investigated.[51] In the high IPFD group, intake of monounsaturated fatty acids was significantly negatively associated with fasting insulin, HOMA-IR, and the metabolic score for insulin resistance (a non-insulin-based index of insulin sensitivity). These associations were independent of sex, age, body mass index, use of anti-diabetic medications, daily energy intake, and recurrence of acute pancreatitis. None of the above associations was statistically significant in the low IPFD or moderate IPFD groups. Further, there were consistently significant differences in the associations between intake of monounsaturated fatty acids and insulin traits in the high IPFD group (but not in the moderate IPFD group) as compared with the low IPFD group. Intake of polyunsaturated or saturated fatty acids did not have a consistent pattern of associations with insulin traits.[51]

Also, a modulating role of IPFD in the acute glucoregulatory effects of ketone-supplemented beverage (the principal ingredient of which was a commercially available β-hydroxybutyrate monoester) in individuals with new-onset pre-diabetes after acute pancreatitis was investigated.[49] This was a secondary endpoint analysis of the CETUS project.[59–64] Individuals with new-onset prediabetes after acute pancreatitis who had similar body mass index and waist circumference were categorised into high IPFD and low IPFD groups. The results showed that, although the ketone-supplemented beverage increased the levels of β-hydroxybutyrate in both individuals with high IPFD and those with low IPFD, the metabolic effects of ketosis on glucoregulatory hormones were dissimilar in the two groups. The ketone-supplemented beverage significantly increased the levels of insulin, C-peptide, and gastric inhibitory polypeptide in individuals with high IPFD. By contrast, it had no significant effect on the above-mentioned hormones in individuals with low IPFD. The levels of glucagon-like peptide 1 were not significantly changed following the intake of the ketone-supplemented beverage in both individuals with high IPFD and those with low IPFD.[49]

IPFD and Biomarkers

Several studies investigated the associations between various substances in blood and IPFD (Table 2). Individuals with pancreatitis were characterised by significant associations of fat in the pancreas with markers of lipid metabolism

Table 2 Circulating Biomarkers of IPFD in Individuals With a History of Pancreatitis

Class of Biomarker	Associated with IPFD	Study ID	Not Associated with IPFD	Study ID
Lipid metabolism	Triglycerides	#5	Low-density lipoprotein cholesterol	#5
	Total cholesterol	#5	High-density lipoprotein cholesterol	#5
Glucose metabolism			Glycated haemoglobin	#1
			Fasting plasma glucose	#1
Pancreatic hormones	Insulin	#1	C-peptide	#1
Gut hormones	Ghrelin	#18	Glucagon-like peptide-1	#1, 18
			Gastric inhibitory polypeptide	#1, 18
			Peptide YY	#18
			Oxyntomodulin	#1, 17, 18
Inflammation	Leptin	#3, 14	Interleukin-6	#3
	Tumour necrosis factor-α	#3	C-C motif chemokine ligand-2	#3
	Lipocalin-2*	#4	C-reactive protein (during hospitalisation for pancreatitis)	#2
			White blood cell count (during hospitalisation for pancreatitis)	#2

(*Continued*)

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Table 2 (Continued).

Class of Biomarker	Associated with IPFD	Study ID	Not Associated with IPFD	Study ID
Iron metabolism	Hepcidin	#20	Ferritin	#20
Pancreatic enzymes	Pancreatic amylase**	#12, 15	Pancreatic lipase (during hospitalisation for pancreatitis)	#2
			Pancreatic lipase	#12, 15
			Chymotrypsin	#12, 15
Others	Periostin	#8	Dipeptidyl peptidase-4	#1
			Total bile acids	#19

Notes: *Lipocalin-2 was significantly associated with high IPFD (ie, binary variable). * * Pancreatic amylase was significantly associated with IPFD only in post-pancreatitis individuals who developed new-onset prediabetes or diabetes. Biomarkers were investigated at the time of magnetic resonance imaging during follow-up (unless otherwise stated). Only biomarkers investigated in fasted state are presented. Indices derived from the studied circulating biomarkers are not presented. Significance of associations was taken from the most advanced statistical model in each individual study.
Abbreviation: IPFD, intra-pancreatic fat deposition.

(triglycerides),[43] iron metabolism (hepcidin),[58] inflammation (tumour necrosis factor-α, leptin, lipocalin-2),[41,42,52] pancreatic and gut hormones (insulin, ghrelin),[39,56] as well as extra-cellular matrix proteins (periostin).[46] The presence of a pro-inflammatory environment in individuals with high IPFD was evident from significant associations of lipocalin-2 with tumour necrosis factor-α,[42] as well as leptin with tumour necrosis factor-α.[41] Some substances were significantly associated with IPFD only in individuals with specific type of pancreatitis: ghrelin – in acute pancreatitis,[56] periostin – in chronic pancreatitis.[46]

Limitations

Several limitations are to be acknowledged. First, given the cross-sectional nature of the studies described in the sections above, inference of causality between IPFD and the investigated parameters cannot be drawn. High-quality prospective longitudinal cohort studies will be essential for understanding how IPFD changes over time and how this affects pancreatitis. Their temporal relationship is warranted to be on the research agenda. Second, the genetic make-up of participants was not investigated. Future studies may consider investigating whether the reported associations are affected by genetic variations. Third, histological confirmation of fat in the pancreas was not available. This is because pancreatic biopsy is highly invasive and it would not have been ethical to perform it in our participants. However, the present study used MRI – the gold standards for non-invasive quantification of intra-pancreatic fat.[12] Fourth, levels of amylase, lipase, and chymotrypsin in the gastrointestinal tract were not measured. Hence, it is unknown whether their circulating and intraluminal levels correlate in our population.[7] Fifth, our single-centre program included a rather limited number of individuals with chronic pancreatitis. This disease is known to have a relatively low incidence and the strict eligibility criteria were used (only individuals with definite CP were included).[65] Last, detailed data on some lifestyle factors (eg, physical activity) that might have affected IPFD were not available.[12] However, all studied individuals were non-athletic and did not report any sudden weight gain or weight loss.

Concluding Remarks

Acute pancreatitis and chronic pancreatitis have substantial burden and the incidence of pancreatitis is projected to increase two-fold from 2020 to 2050, with the average annual growth of 2.4%.[66–69] There is no routinely available treatment that targets a specific element in the pathogenesis of pancreatitis, at least in part because of an incomplete understanding of what causes pancreatitis.[12,70,71] The PANDORA hypothesis theorised the key role of high IPFD in both acute pancreatitis and chronic pancreatitis.[12] Two complementary COSMOS systematic reviews published in 2017 identified no clinical study of IPFD (determined with the use of MRI) in relation to pancreatitis.[18,19] Because of this glaring gap in knowledge, 3.0 T MRI-determined IPFD became a flagship direction of the COSMOS program in the

ensuing years. The 20 clinical studies described in the sections above provided the much-needed foundational knowledge on IPFD in the context of pancreatitis (Figure 2).

In 2024, two complementary studies took the findings of the COSMOS program to the next level.[72] Yamazaki and colleagues conducted a Mendelian randomisation study involving 25,617 individuals.[73] They established that higher IPFD was associated with significantly greater risks of both acute pancreatitis and chronic pancreatitis. Importantly, this association was causal as genetic variants (forming the basis for Mendelian randomisation studies) are fixed at

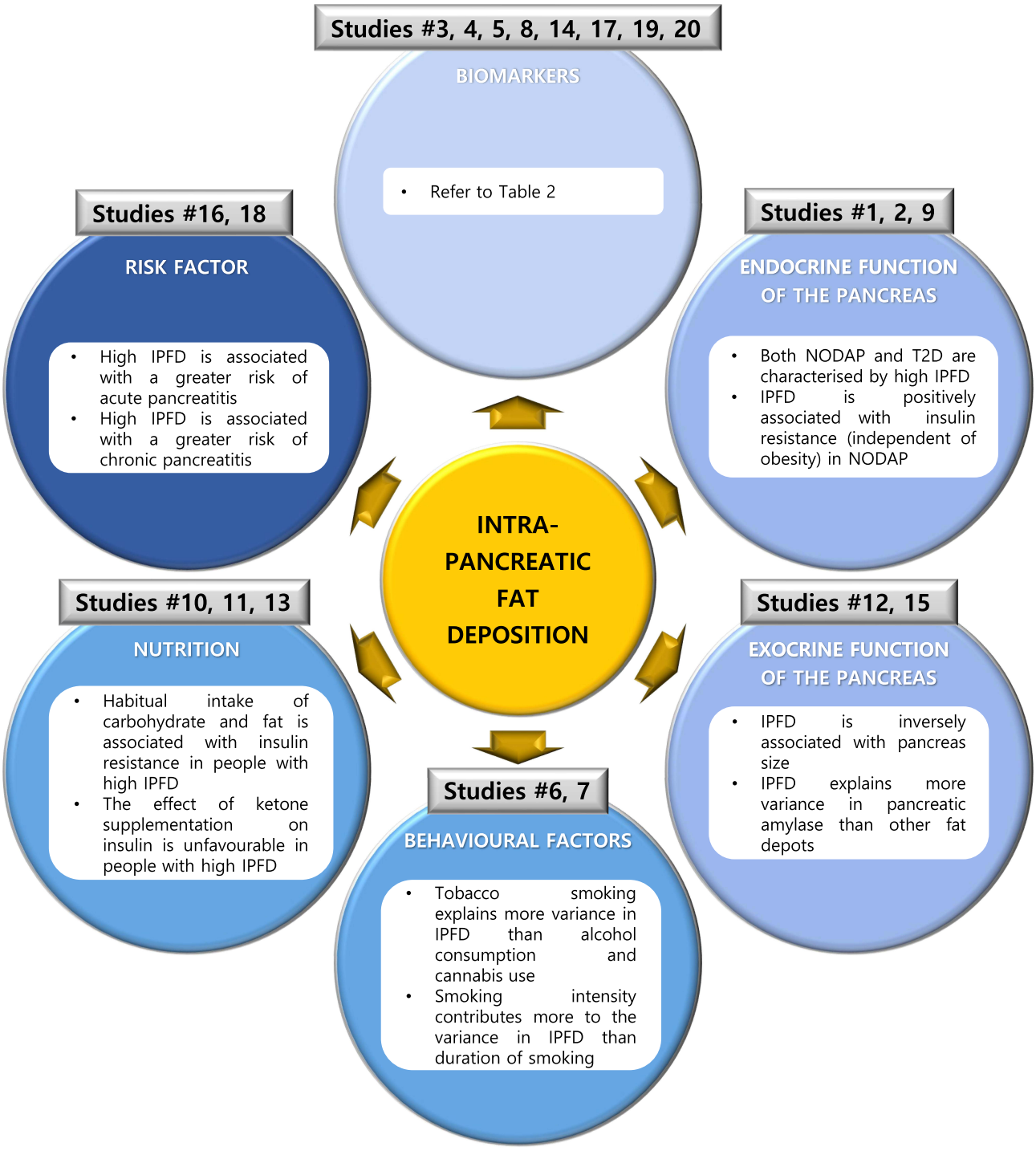

Figure 2 Key findings from the COSMOS program.

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conception. Further, the association was unidirectional as there was no evidence of reverse causation (ie, pancreatitis leading to higher IPFD).[73] Dong and colleagues conducted a prospective longitudinal cohort study involving 42,599 individuals.[74] They showed that higher IPFD at baseline was associated with a significantly higher risk of acute pancreatitis during nearly 5 years of follow-up. This held true after adjustment for age, sex, body mass index, hepatic fat content, tobacco smoking, alcohol consumption, and other covariates. Also, the findings were internally consistent as both the analysis according to quintiles of IPFD and the analysis according to age-specific and sex-specific upper limits of normal for IPFD yielded similar results.[74]

The novel clinical insights into IPFD derived from the COSMOS program (as well as other high-quality investigations) bring the field closer to a comprehensive and integrated approach to primary, secondary, and tertiary prevention of pancreatitis through apposite interventions.[66,75,76] Mechanistic research will help uncover the specific pathways linking IPFD to acute pancreatitis and chronic pancreatitis, potentially guiding the development of targeted treatments.

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Disclosure

The authors declare no conflicts of interest in this work.

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