
Body composition in surgical disease of the gastrointestinal tract

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Abstract

Background

The dynamic metabolic, endocrine and immune properties of adipose and muscle tissue are increasingly being implicated in disease pathology. The aetiologies of diverticular disease, and of pancreatic cancer have not been fully described. However, it seems that dysregulation in inflammatory pathways, associated with changes in body composition, is associated with both diseases.

Aims

This thesis aims to explore the relationships between body composition and these two intraabdominal pathologies: diverticular disease and pancreatic cancer. It also aims to examine the potential for understanding of individual body composition phenotype to better understand these diseases.

Methods

A review of the current literature was performed. In the retrospective studies, searches of the radiology database and hospital records with International Classification of Disease coding were used to identify patients. In the prospective work, patients were recruited at the time of diagnostic biopsy. Reviews of medical records were used to identify demographic, disease and treatment information. Computed tomography scans from routine clinical care of patients were used for all body composition analysis.

Results

Diverticular disease was associated with increased levels of visceral adipose tissue. There was a lower incidence of metformin use in diabetics with diverticulitis, compared to diabetics with diverticulosis.

Metastatic pancreatic neuroendocrine tumours (PNET) were associated with lower adipose tissue, but no difference in skeletal muscle mass, compared to those with local PNET at diagnosis. There was a high incidence of myopenia, sarcopenia and symptoms associated with anorexia in patients at the diagnosis of pancreatic ductal adenocarcinoma (PDAC). There was no association between gemcitabine nab paclitaxel dose to skeletal muscle area ratio, and toxicity, in PDAC.

Conclusion

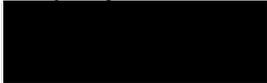
Body composition abnormalities were associated with both diverticular disease and pancreatic cancer.

Declaration

This thesis was prepared in accordance with the guidelines of the Monash University combined Bachelor of Medicine/Bachelor of Surgery (MBBS) and Doctor of Philosophy degree. To the best of my knowledge and belief this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

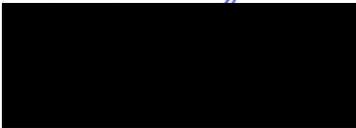
This thesis includes an original paper published in a peer-reviewed journal and two unpublished publications. The core theme of the thesis is body composition in gastrointestinal disease. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the School of Clinical Sciences, Monash University under the supervision of Mr Daniel Croagh and Dr Gregory Moore. The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research. In the case of *chapters 3 and 5* my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
3	Metformin use in diabetics with diverticular disease is associated with reduced incidence of diverticulitis	Published	70% Study design, data collection and analysis, drafting of manuscript	J Evans (10%: Data collection) D Croagh, G Moore (Jointly 20%: Study design, critical review of manuscript)	Yes
3	Body composition differences in diverticular disease	Submitted	70% Study design, body composition analysis, data collection and analysis, drafting of manuscript	DQ Holt (5%: critical review of manuscript) A Borsaru (5%: grading of diverticulitis severity) S Gwini (2%: statistical advice) D Croagh (5%: critical review of manuscript) G Moore (23%: study design, critical review of manuscript)	No
5	Gemcitabine nab-paclitaxel toxicity is not associated with body composition in pancreatic cancer	Submitted	70% Study design, body composition analysis, data collection and analysis, drafting of manuscript	D Croagh, G Moore (Jointly 15%: study design, critical review of manuscript) A Fox, R Wong, M Lee (Jointly 10%: contribution of patients, review of manuscript) D Holt (5%: review of manuscript)	No

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Date: 14/10/2017

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

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3. Sandhu M, Freckelton J, Evans JA, Shelton E, Moore GT. The association between visceral fat and resection length in operative Crohn's disease: A 10-year experience at a single tertiary metropolitan hospital. *Journal of Gastroenterology and Hepatology*. 2017;32:121-54
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List of abbreviations

PNET	Pancreatic neuroendocrine tumour	US	Ultrasound
PDAC	Pancreatic ductal adenocarcinoma	MRI	Magnetic resonance imaging
BMI	Body mass index	CCF	Congestive cardiac failure
CT	Computed tomography	VAT	Visceral adipose tissue
HU	Hounsfield unit	PanIN	Pancreatic intraepithelial neoplasia
L3	Lumbar spinal level 3	IPMN	Intraductal papillary mucinous neoplasm
VFL	Visceral fat level	MCN	Mucinous cystic neoplasm
DXA	Dual-energy X-ray absorptiometry	COX	cyclooxygenase
SCFA	Subcutaneous fat area	PaSC	Pancreatic stellate cells
VFA	Visceral fat area	MMPS	metalloproteinases
CRP	C-reactive protein	TIMMPS	Tissue inhibitors of metalloproteinases
IL-6	Interleukin 6	5-FU	5-Flurouracil
TNF- α	Tumour necrosis factor alpha	DNA	Deoxyribonucleic acid
CD	Cluster of differentiation	FOLFIRINOX	Fluorouracil, irinotecan, oxaliplatin, and leucovorin
T2DM	Type 2 diabetes mellitus	NF-PNET	Non-functioning pancreatic neuroendocrine tumour
IHD	Ischemic heart disease	MEN-1	Multiple endocrine neoplasia type 1
LPS	Lipopolysaccharide	BSA	Body surface area
IL-1	Interleukin 1	PEF	Peak expiratory flow
EWGSOP	European Working Group on Sarcopenia in Older People	EMCF	Extramyocellular fat
IWGS	International Working Group on Sarcopenia	SMI	Skeletal muscle index
CASCO	Cachexia score	IQR	Interquartile range
mRNA	Messenger ribonucleic acid	TFA	Total fat area
IGF-1	Insulin like growth factor 1	N	Number
LGIT	Lower gastrointestinal tract	HGS	Handgrip strength
NSAID	Nonsteroidal anti-inflammatory drug	Gem-Nab-P	Gemcitabine nab-paclitaxel
SUDD	Symptomatic uncomplicated diverticular disease	MST	Malnutrition Screening Tool

Chapter 1: Introduction

In 1965, Josef Brozek described the “menacingly” rapid growth of literature on body composition.¹ Since 1965 there has been a sharp acceleration in growth of work in this complex field. It is now clear that muscle and adipose tissue are not just indolent, structural energy depositions; rather they play a complex role in hormonal and metabolic homeostasis. In disease states this homeostasis is disrupted, often both locally in the affected and surrounding tissues, as well as systemically. Firstly, this thesis explores the relationships between body composition and two intraabdominal pathologies: diverticular disease and pancreatic malignancy. It then goes on to examine the potential for understanding of unique body composition phenotype to provide personalised treatment to patients with these diseases. While the 21st century has brought exciting developments in the management of many gastrointestinal conditions, despite their growing prevalence, there has been little progress in the treatment of diverticular disease and pancreatic cancers.

While a number of risk factors for diverticular disease have been established, the pathogenesis of this disease remains elusive. There is evidence suggesting that it lies with dysregulation of inflammatory pathways in the colon. We propose that increased visceral adipose tissue, which, in excess, produces inflammatory cytokines, may produce an environment that propagates diverticular disease. This would explain the association between obesity and diverticular disease. Metformin has been shown to reduce systemic and colonic inflammation, and is an effective therapy for other diseases associated with increased visceral adipose tissue and dysregulation of intra-abdominal inflammation.

Significant interplay between cancers and adipose and muscle tissues has been demonstrated. This is particularly important in pancreatic malignancies, due the pancreas' critical role in metabolism. Obesity has been identified as a risk factor for pancreatic cancer, and weight loss during the progression of disease is particularly characteristic of pancreatic cancer. While there is a paucity of literature examining body composition in pancreatic neuroendocrine tumours (PNET), there is a significant body of work in relation to pancreatic ductal adenocarcinomas (PDAC). In particular, low lean mass has emerged as a predictor of poor outcomes: survival and chemotherapy toxicity. The reasons for this have still not been fully elucidated. It is possible that changes in body composition affect the volume of distribution of chemotherapy agents, dependent on the extent to which they are hydro or lipophilic.

With the development of cross sectional imaging based body composition analysis tools, there has been a substantial increase in the evidence in this area. However, intrinsic to scientific research, with growth of understanding, comes an exponential increase in avenues for further exploration. This thesis is designed to provide small building blocks, in the area of gastrointestinal disease, to fill gaps in this “menacingly” rapidly growing metaphorical wall.

The following chapters constitute a hybrid thesis comprised of published, and non-published material. They investigate body composition and gastrointestinal disease. First is a literature review, which does not cover all aspects of these areas comprehensively, but aims to provide context for the subsequent data chapters. The data chapters involve study of the relationship between body composition and disease status, in diverticular disease and pancreatic malignancy, and the use of body composition phenotype, and its associated inflammation, to target treatment. Due to the style of the thesis,

discussion of results occurs within each chapter. So, instead of the traditional discussion and conclusion chapter, the thesis ends with a brief summation of findings and compilation of pertinent discussion points.

Chapter 2: Literature review

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2.1 Body composition

Body composition is a term used to describe the proportions of adipose tissue, muscle and bone in the body. Body Mass Index (BMI), an anthropometric measurement calculated using a patient's height and weight (weight (kg) / height (m)²), is often used to estimate body composition and predict likelihood of disease. However, in many patients BMI is a poor marker of actual body composition, and thus poorly measures contribution of lean and adipose tissue to the pathogenesis of disease and the effect of disease on these tissue types. As we gain increasing levels of understanding of the dynamic immune and endocrine functions of body tissues and their impact on human physiology, BMI has become increasingly inadequate as a body composition estimation tool for the use in both research and the clinic. This review will focus on visceral adipose tissue, the adipose tissue that lies within the abdominal cavity, ectopic fat and skeletal muscle.

Body Composition Measurement

The advent of single slice computed tomography (CT) body composition analysis tools has allowed for precise, non-interventional quantification of individual muscle and adipose compartments.^{2,3} This technology identifies all tissue within a user-specified radio-attenuation boundary, allowing the user to select each tissue compartment manually, based on anatomical location, and measure its cross-sectional area (figure 1). The Hounsfield unit (HU) thresholds -190 to -130 have been shown to best identify visceral and extramyocellular fat, and -150 to -50 to identify subcutaneous fat. Using the thresholds -20 to +150 HU identifies skeletal muscle.² The cross sectional tissue areas from a single CT slice at lumbar spinal level 3 (L3) have been shown to be representative of the total body volumes of each tissue compartment.²

Previously anthropometric measurements involving height, weight, waist and hip circumferences, and skin folds have been used to estimate visceral and subcutaneous fat levels (VFL). These techniques are non-invasive and readily accessible, but they can be inaccurate, especially at the extremes of ages and BMI levels.⁴

Bioelectrical impedance is also non-invasive and is readily commercially available as an adjunct to bodyweight scales. While it can provide measurement of total body adipose tissue, bioelectrical impedance is not able to differentiate between subcutaneous, ectopic and visceral adipose tissue.

Finally, dual-energy X-ray absorptiometry (DXA) is considered the 'gold standard' body composition analysis tool. It uses a very low dose of radiation, and is well-validated and provides accurate and reproducible results.⁵ However, DXA is an uncommon clinical imaging modality in many conditions, limiting the ability for it to be used as a body composition analysis tool in retrospective, or observational research.

Adipose tissue

Adipose tissue is no longer considered to be an inert form of energy storage; rather it is becoming increasingly clear that it functions as a dynamic endocrine and immune organ, which is able both to respond to and influence a number of metabolic and inflammatory pathways. The bioactive peptides expressed and secreted by adipose tissue, known as adipokines, are integrally involved in the mediation of processes including energy metabolism, neuroendocrine function and immune function.⁶ This important role is highlighted in obesity, when excess adipose tissue is associated with insulin

resistance and hyperglycaemia, dyslipidaemia, hypertension, and prothrombotic and proinflammatory states.⁶

The sub-clinical inflammatory state seen in obesity has been associated with a number of pro-inflammatory cells. Firstly, the inflammatory marker C-reactive protein (CRP) is increased in obese individuals when compared to lean individuals; however, it is not raised to the extent seen in acute inflammatory processes.⁷ CRP production in the liver is up-regulated by the inflammatory cytokine interleukin-6 (IL-6), and so serves as a proxy marker for circulating levels of IL-6.⁸ Secondly, the adipose tissue content of cluster of differentiation 14 (CD14⁺) and CD31⁺ macrophages, which act as immune cell recruiters, is positively correlated with BMI, with the highest levels seen in obese individuals.⁹ Thirdly, and also involved with the inflammatory cascade, the pro-inflammatory cytokines tumour necrosis factor alpha (TNF- α) and IL-6 are seen in abnormally high concentrations in obesity. Both of these cytokines have been shown to increase with BMI, waist circumference and visceral adipose tissue levels.¹⁰ Whether there is a causal nexus between visceral adipose tissue and non-infectious inflammation is unclear. It certainly seems to be associated with the syndrome, but whether it actually causes metabolic disease is not finally resolved.¹¹

Leptin

Leptin is an polypeptide adipokine which plays a critical, but complex role in appetite regulation,¹² and is increasingly understood to be involved in immune function. Leptin is produced by adipose tissue, so when adipose tissue stores are low, so are leptin levels, resulting in lower binding to the leptin receptors in the brain stimulating hunger and simultaneously reducing energy expenditure, to maintain body weight. However, in obese states this pathway is disrupted. While leptin levels are elevated in obesity,¹³ this does not necessarily result in a corresponding reduction in appetite and increase in

energy expenditure, because obesity is also associated with a hypothalamic leptin resistance.¹⁴ While there are a number of theories that describe potential mechanisms that result in leptin resistance, the cascade of events is incompletely understood.¹⁵ Leptin also plays a critical role in the modulation of inflammation, exhibiting pro-inflammatory effects. Leptin has been shown to up-regulate the production of pro-inflammatory cytokine IL-2, and inhibit the production of anti-inflammatory IL-4 by T-cells.¹⁶

Adiponectin

Adiponectin, a 30 kDa protein, was first described in 1995 by Scherer as “exclusively produced by adipocytes”, and abundant in plasma.¹⁷ It has since become well established that there is a strongly negative correlation between adipose tissue and plasma adiponectin levels in humans, with weight loss increasing plasma levels and weight gain, particularly in obese individuals, decreasing adiponectin.¹⁸ Notably, a reduction in adiponectin appears to play a role in the pathogenesis of type-2 diabetes mellitus (T2DM). Adiponectin functions as an insulin sensitizer by inhibiting the hepatic production of glucose in addition to increasing hepatic and skeletal muscle fatty acid oxidation.¹⁹ Adiponectin has become increasingly relevant in cardio-vascular disease because, in addition to its role in T2DM, it is also involved in the inhibition of macrophages to blood vessel endothelium, which is a necessary step in the development of ischaemic heart disease (IHD). In terms of inflammation, adiponectin strongly inhibits the secretion of TNF- α in adipose tissue, leading to increased TNF- α secretion in obese individuals.²⁰ It does not, however, appear to affect plasma levels of TNF- α .²⁰

TNF-Alpha

Increased expression of TNF- α is seen in diverticulitis. Interestingly increased expression of TNF- α is also seen as adipose tissue levels increase in humans. This was demonstrated by Winkler et al. who measured levels of both

subcutaneous and visceral adipose tissue, and TNF- α in 43 patients, finding “significantly higher levels of TNF- α in the obese sub-group”.²¹ Although this study had a small sample group the result is supported by the 2001 study of Kern et al., which found a 7.5 fold increase of adipose TNF- α expression in obese individuals when compared to lean (BMI<25) individuals.²²

In addition to adipose expression, serum levels of TNF- α have also been demonstrated to be higher in obese patients, correlating to increasing levels of visceral adipose tissue.²² Increased levels of TNF- α have been implicated in diverticular disease, particularly acute diverticulitis,²³ as well as cancer cachexia.²⁴

Interleukin-6

IL-6 has been labelled both an adipokine and a myokine, because of its secretion from both adipose tissue and skeletal muscle, and its role in mediating peripheral and central organ function.²⁵ Secretion of IL-6, however, is not limited to these tissues; it is also released from fibroblasts, osteoblasts, pancreatic β cells, endothelium and keratinocytes.²⁶ IL-6 has a complex, incompletely understood role in the inflammatory cascade; it is involved in secretion of TNF- α and IL-6 itself, mediation of B cell, T cell and macrophage function, while also involved in the attenuation of the inflammatory cascade, it is classed as both a pro and anti inflammatory cytokine.²⁵ In isolated models, visceral adipose tissue has been shown to produce more IL-6 than subcutaneous adipose tissue.²⁷ There is consensus that IL-6 levels are increased in obesity, as part of the chronic, subclinical inflammatory state. However, the full impact that this has on organ function, and the development of inflammatory conditions such as diverticulitis, has not been fully elucidated.

Visceral Adipose Tissue and Gut Microbiota

There is growing evidence that obese individuals have a different composition of gut microbiota when compared to lean individuals. A number of animal models²⁸⁻²⁹⁻³¹ and human studies^{32,33} have identified increased prevalence of *Firmicutes* and reduced levels of *Bacteroidetes* in obese states. The levels of these bacterial groups normalise with weight loss.³² Increased populations of *Akkermansia* are also associated with a favourable metabolic profile in cross sectional analysis comparing obese patients, and patients with T2DM, to healthy lean controls.³⁴ This has been further studied using an animal model, where changes in *Akkermansia* population levels were associated with the onset of inflammation and metabolic dysfunction, in mice fed a high fat diet.³⁵ These studies are interesting, however their design is insufficient to demonstrate a cause effect relationship. While the role gut microbiota play in obesity and insulin resistance is still not clear, it has been suggested that the populations of bacteria which are up-regulated in obesity, may alter the permeability of the bowel, allowing endotoxins to cause a low grade inflammation. This hypothesis was tested using bacterial lipopolysaccharide (LPS), which is also increased in obesity, as a model in mice. Mice with artificially increased LPS developed increased expression of inflammatory cytokines interleukin 1 (IL-1), IL-6 and TNF- α .³⁶

Ectopic Fat

Ectopic fat describes depositions of triglycerides outside of the subcutaneous and visceral fat compartments. Intrahepatic fat, and inter and intramuscular fat appear to be able to produce not only local effects, but also have a systemic metabolic effect.³⁷⁻³⁹ This review will only discuss muscular fat, as intrahepatic fat is beyond the scope of the study.

Myosteatorsis

The terminology used to describe the storage of fat cells in muscle is not well defined and at times used interchangeably in the academic literature.

Myosteatorsis describes the fatty infiltration of skeletal muscle. For the purpose of this review we will be using 'intermuscular fat' to describe adipose tissue deposits beneath the deep fascia between muscle groups and 'intramuscular fat' to describe the deposits within muscles.

Extent of myosteatorsis is positively associated with BMI.⁴⁰ Increased levels of inter and intramuscular fat is, independently of BMI, associated with both local tissue and systemic insulin insufficiency.^{41, 42} Whether intermuscular fat acts as a marker of metabolic dysfunction, or whether it plays a causative role has not been fully elucidated.⁴³ It is possible that the link between metabolic dysfunction and myosteatorsis lies with systemic inflammation. Similarly to visceral adiposity, high levels of myosteatorsis, independently of BMI, have been associated with increased inflammatory markers CRP and IL-6.⁴⁴⁻⁴⁶

Skeletal Muscle

Muscle Function Testing

Hand Grip Strength

Handgrip testing using a dynamometer is a well-validated tool to assess muscle strength. There is a significant body of literature that demonstrates an association between reduced grip strength and poor clinical outcomes,⁴⁷ including: increased length of stay,⁴⁸ functional decline,⁴⁸ morbidity⁴⁹ and mortality.⁵⁰ The method by which grip strength is assessed is not consistent,⁴⁷ with right hand,⁵¹ dominant hand,⁵² non-dominant hand⁵³ and strongest hand⁵⁴ all used. Dynamometers are inexpensive, portable, easy to use, and achieve reproducible results, making them an appropriate tool for strength testing both clinically and in research.

Peak Expiratory Flow

The use of peak expiratory flow measurement as a test for muscle strength has been used but is not so well validated. An association has been demonstrated between muscle strength and peak expiratory flow rate by one study.⁵⁵ The European Working Group on Sarcopenia in Older People (EWGSOP) suggest that more research on peak expiratory flow rate is required before it can be recommended as a standard prognostic tool.⁵⁶

Sarcopenia

Definition

The term 'sarcopenia' is derived from the Latin 'sarx' meaning flesh and 'poenia' meaning loss. Rosenberg first coined it in 1989 to describe the age related reduction in lean body mass that he saw as critical in the increasing levels of morbidity associated with aging.⁵⁷ Use of the term sarcopenia has evolved to encompass both reduced levels of absolute muscle mass as well as a poor muscle performance. The exact definition, however, is contentious. A number of efforts have been made in the last decade to construct a universal definition to provide continuity in the academic literature. While the criteria produced by the EWGSOP,⁵⁶ the International Working Group on Sarcopenia (IWGS)⁵⁸ and the Society of Sarcopenia, Cachexia and Wasting Disorders⁵⁹ were not in total agreement, they did all concur that sarcopenia should be described not only in terms of skeletal muscle volume, but also in terms of muscle function. For this reason, throughout this thesis, the term myopenia will be used to describe the isolated finding of low skeletal muscle volume, and sarcopenia, in line with these international guidelines, will only be used in the presence of both myopenia *and* reduced muscle function.

Recent studies have identified a disassociation between proportion of muscle loss and proportion of loss of muscle strength. Muscle strength has also been identified as an independent predictor of falls and mortality. For these

reasons, it has been suggested that muscle performance is separated to become its own entity ‘dynapenia’ leaving sarcopenia to describe just the scarcity of muscle mass. However, in light of the consensus between the major working groups described above regarding the definition of sarcopenia, this review will use a definition of sarcopenia that requires both reduced muscle mass and reduced muscle function.

Diagnostic Criteria

A number of differing sets of criteria have been used to define sarcopenia in the academic literature, each of which produce vastly different prevalences of sarcopenia within a given cohort.⁶⁰ This has resulted in a body of literature that is difficult to synthesise and translate into clinical practice. In light of this deficiency, the IWGS and the EWGSOP were each formed to produce a standardised set of criteria for sarcopenia. Unfortunately, the groups produced two sets of criteria that only have a “fair” correlation ($\kappa=0.448$).⁶¹

The criteria designed by EWGSOP require evidence of low muscle mass in association with either (or both) low muscle strength or low physical performance.⁵⁶ The EWGSOP criteria also allow for staging of sarcopenia, providing a more versatile research tool (table 1), and so, for this reason, will be used for this study.

EWGSOP conceptual stages of sarcopenia

Stage	Muscle mass	Muscle strength	Performance
Presarcopenia	↓		
Sarcopenia	↓	↓	Or ↓
Severe sarcopenia	↓	↓	↓

Table 1 Sarcopenia: European consensus on definition and diagnosis⁵⁶

Cachexia

Definition

The term cachexia comes from the Greek words 'kakos' - bad and 'hexis' - condition. It is used to describe a syndrome of pathological weight loss that characterises a number of medical conditions. Similarly to sarcopenia, until recently, there has not been a consensus definition or set of diagnostic criteria for cachexia. In 2011 an international group was formed to correct this, providing a framework for consistency in this area of academia. They described cancer cachexia as the progressive loss of skeletal muscle mass which "cannot be fully reversed by conventional nutritional support", that causes a reduction in physical function in cancer patients.⁶² This definition is largely in agreement with an earlier definition produced by Fearon et al.⁶³ It does differ, however, by not including reduced appetite and evidence of systemic inflammation (elevated serum levels of C-reactive protein), as central and defining features, as Fearon et al did in their 2006 definition of cachexia.⁶³

Diagnostic Criteria

The same international group produced a set of diagnostic criteria for cancer cachexia. Patients with at least a 5% total body weight reduction within 6 months are defined as cachectic. For patients who are initially underweight, have a BMI of less than 20 or have a skeletal muscle index which is consistent with sarcopenia, a weight loss of 2% of total body weight or more is considered cachectic.⁶² In 2011, Blum et al sought to validate the use of reduction in BMI to categorise cachexia, using the ability to predict reduced mean survival time to measure the 'success' of the tool. They found that when used as a binary tool, patients sorted into groups that had, or did not have cachexia; BMI loss was sufficient to predict poor outcomes. However, when

extended to a four group model including also 'pre-cachexia' and refractory cachexia, BMI failed to adequately distinguish between the groups. Blum et al suggested that CRP and anorexia scores might define the pre-cachexia group better.⁶⁴

The cachexia score (CASCO) has been developed more recently and encompasses changes in lean and total body mass, inflammatory and metabolic disturbances, physical functional capacity and quality of life assessment.⁶⁵ This scoring system is yet to be validated as a research or clinical tool.

Pathophysiology of Muscle Loss

Cachexia and sarcopenia are the result of an imbalance between muscle protein synthesis and muscle protein breakdown. The mechanism behind the pathological muscle loss that defines both conditions has not been fully defined.

The loss of lean mass described by these conditions is distinct from the weight loss seen in starvation. In states of starvation, which is defined as pure caloric deficiency, adaptive processes occur to ensure maintenance of lean tissue mass, by increasing the metabolism of adipose tissue.^{66, 67} This suggests that a complete explanation of the cause of cachexia and sarcopenia lies beyond just an energy intake and output imbalance and lies with a multifactorial process, involving a complex interplay between not only caloric input and output, but also genetic, endocrine, metabolic and inflammatory pathways.

This review will first discuss the genetic, environmental, inflammatory and hormonal factors that may contribute to the selective loss of skeletal muscle that characterises cachectic and sarcopenic states. It will later discuss the

factors that contribute towards a negative energy balance: anorexia, malabsorption and hypermetabolism in cancer patients.

Inflammation

It appears that the systemic low-grade inflammation that characterises a large number of malignant and gastrointestinal disease states, plays a role in pathological muscle break down. This relationship has been examined in observational human studies as well as in animal models.

Large longitudinal human studies found an association between increased levels of the inflammatory marker CRP and the inflammatory cytokines TNF- α and IL-6, and incidence of muscle weakness.^{68, 69} High levels of CRP, TNF- α and IL-6 are also associated with advanced pancreatic cancer.⁷⁰

The positive association between sarcopenia and TNF- α is consistent with a mouse model conducted by Cai et al. in 2004, which demonstrated the molecular mechanism behind this association. It showed that TNF- α down regulates the expression of MyoD messenger ribonucleic acid (mRNA). This transcription factor is directly responsible for the stimulation of production of myogenic proteins. So, in this way, a reduction in MyoD mRNA leads to muscle wasting.⁷¹

The role of IL-6 in muscle loss has also been assessed using a mouse model. IL-6 inhibits insulin like growth factor 1 (IGF-1),⁷² which is a modulator of muscle mass.⁷³ IGF-1 has been shown to phosphorylate the S6K1 molecule. S6K1 has the ability to induce skeletal muscle hypertrophy.⁷⁴ Haddad et al. demonstrated that infusing small levels of IL-6 (equivalent to those associated with aging) into a mouse results in a reduction in skeletal muscle mass as well as a reduction in the phosphorylation of S6K1.⁷⁵ This model supports the evidence that IL-6, through its interactions with IGF-1 and therefore S6K1,

plays a role in the modulation of skeletal muscle mass, implicating inflammation in the pathogenesis of muscle loss.

The role of inflammation in muscle wasting is further supported by an animal study that demonstrated a reduction in muscle loss when mice, which had naturally developed a low-grade inflammatory state with old age, when treated with the anti-inflammatory drug ibuprofen.⁷⁶ The ability to inhibit muscle loss by targeting the inflammatory response, suggests that not only is inflammation associated with cachexia and sarcopenia, but that it plays a causative role. The protective effect of ibuprofen on muscle mass has not yet been replicated in humans. Interestingly, coffee treatment, which has well-established anti-inflammatory effects, has been shown, also in a mouse model, to increase muscle mass and muscle performance.⁷⁷

2.2 Diverticular Disease

Descriptions of colonic diverticula date back to the 1700s, characterised by Alexis Littre as “a condition of saccular out-pouchings of the colon”⁷⁸ The terminology used to describe the various manifestations of diverticular disease is often poorly defined and used interchangeably in the academic literature. For the purposes of this review diverticulosis will be used to describe the presence of diverticula in the colon. Diverticular disease implies that there are symptoms associated with the diverticulosis. Diverticulitis will be used to describe the presence of macroscopic evidence, either on radiological imaging or colonoscopy, of inflammation of one or more diverticula.

The exact prevalence of diverticulosis is not known because most patients are asymptomatic. However, it is estimated that the percentage of people affected in Western populations increases from 5% at age 40 to 65% at age 80.⁷⁸⁻⁸⁰

The left sided colonic diverticula seen in Western patients are in fact pseudodiverticula; the mucosal layers of the bowel wall herniate out through the weaker sections of the muscle layer where blood vessels perforate through to supply the wall.⁸¹ This is in contrast to the right-sided diverticula, more common in East Asian patients, which tend to be ‘true’ diverticula, with all layers of the bowel wall bulging outwards.⁸¹

Pathophysiology

The wall of the colon has two complete muscular layers referred to collectively as the muscularis propria; the circular layer completely circumscribes the lumen, whereas the longitudinal layer is in the form of three taeniae coli.⁸² The vessels supplying blood from the mesentery to the mucosal and submucosal layers of the colon wall, the vasa recta, perforate through the muscularis propria in order to reach these layers, creating points

of microscopic atrophy. It is at these sites of weakening that the mucosal bulging, diverticula, are found in patients with left-sided diverticulosis.⁸³ However, the exact pathogenesis of diverticulosis is incompletely understood. In the last three decades large population-based studies have led the scientific community to reassess the dogmas of the twentieth century and form new hypotheses regarding both the formation of colonic diverticula as well as the causal and precipitating factors in diverticulitis.

Diet

There have been a number of theories regarding the role particular dietary and other lifestyle factors play in the development of diverticulosis, as well as its complications. The evidence surrounding these theories is contradictory, with large cohort studies casting doubts on the theories of the last century. The hypothesis that a low fibre diet was a causal factor in diverticular disease was first advanced in 1971.⁸⁴ This is supported by a number of epidemiological associations. Diverticular disease is more common in Western communities in which the average fibre intake is significantly lower than in developing countries in Asia and Africa. The key criticism of this observation-based theory is that it fails to account for the different spectrum of age groups in the respective communities; Western communities have a significantly greater life expectancy than those of Africa and Asia in the 1970s, and therefore a greater proportion of the population over 50.⁸⁴ As diverticular disease is strongly associated with increasing age, this oversight may have acted as a confounder. However, this theory is supported by the observation that when people from these areas begin to adopt a Western diet, their risk of diverticular disease increases.⁸⁵ In addition, vegetarians were found to have comparatively high fibre intake when compared to non-vegetarians and were also less likely to be hospitalised by or die from diverticular disease.⁸⁶ Animal models involving rats on a diet deplete of fibre also supported a causal link

with diverticulosis.^{87,88} For these reasons recommendations surrounding fibre intake formed the basis of lifestyle recommendations in the prevention and management of diverticular disease in the second half of the 20th century. However, a large population study contradicts this theory, reporting that not only is diverticulosis not associated with a low fibre diet, in fact the obverse appears to be true; a high fibre diet is associated with higher prevalence of the disease.⁸⁹

The decrease in fibre seen with the industrialisation of the West was accompanied by increased red meat consumption. There have been a number of observational studies that examined the relationship between a diet containing red meat and the presence and severity of diverticular disease. These cross-sectional studies report conflicting results. In terms of left-sided colonic diverticulosis, the role red meat consumption plays remains unclear; one large cohort study found that there was no association between red meat consumption and diverticulosis,⁸⁹ whereas two other studies found higher rates of symptomatic diverticular disease,⁹⁰ and hospitalisation with diverticular disease,⁹¹ in red-meat-eating patients. Right-sided colonic diverticulosis on the other hand, appears to be strongly correlated with red meat consumption, with one study producing an odds ratio of 24.8.⁹² In terms of other lifestyle factors, smoking,⁹³ physical activity⁸⁹ and obesity⁹³ do not appear to be related to risk of diverticula formation. Alcohol consumption, however, correlates positively with diverticulosis.⁹³ The evidence of alcohol as a risk factor for diverticulosis is retrospective epidemiological evidence, which is not able to prove causation. It is plausible that it is the obesity, and more specifically increased levels of visceral adipose tissue associated with high levels of alcohol consumption,⁹⁴⁻⁹⁶ that predisposes individuals to diverticulosis. It is important to note that much of the information surrounding these lifestyle factors has been derived from a

Korean study.⁹³ While the role of genetics in diverticular disease has not been fully elucidated, it does appear that there are differing trends amongst ethnic groups. For this reason, the results of the Korean study may be limited in its relevance for other populations.

Type 2 Diabetes Mellitus

Epidemiologically, diabetes is also associated with the western lifestyle. The evidence on the role of T2DM in the pathogenesis of diverticulosis remains unclear. The two largest population-based studies present conflicting data on the prevalence of diverticulosis in patients with T2DM, when compared to normoglycaemic patients, with one identifying T2DM as a protective factor in terms of the development of diverticula,⁹⁷ and the other demonstrating a higher rate of diverticulosis in patients with T2DM.⁹⁸

Connective Tissue

Diverticulosis is significantly more common in patients with connective tissue disorders such as Ehlers Danlos syndrome,⁹⁹ Marfan syndrome¹⁰⁰ and polycystic kidney disease,¹⁰¹ than the general population. This suggests that abnormalities in the make up of an individual's connective tissues may predispose them to the formation of diverticula. This is supported by a number of studies that have identified changes in the structure of the colonic muscular layers on microscopic examination. It appears that patients with diverticular disease have an elastin content in the outer muscular layer which is double that of a healthy control.¹⁰² The collagen also appears to be deranged in diverticulosis. While overall collagen levels appear to be normal in diverticulosis, type 2 collagen is overexpressed in affected patients.¹⁰³ There is also increased cross-linking of collagen.¹⁰⁴ Increased cross-linking of collagen in muscular tissue is associated with ageing,¹⁰⁵ which may help to explain the association between diverticular disease and increasing age.

Genetics

The role that genetics play in the development of diverticulosis and its complications is not fully elucidated. The strong association seen between diverticulosis and the genetic connective tissue conditions discussed above suggests that there is, at least in part, a heritable component to diverticulosis. A 2013 population-based study of siblings and twins found strong evidence for a heritable component in the aetiology of diverticulosis. Siblings of cases were three times more likely to develop the condition than the general population. Monozygotic twin pairs were also more likely to display disease status similarity and dizygotic twin pairs.¹⁰⁶ These results replicate those of a similar Swedish population based twin study, which found close to double the disease status concordance in monozygotic twin pairs, when compared to dizygotic.¹⁰⁷

Complications of Diverticular Disease

Diverticular Bleeding

Diverticular bleeding represents 17-40%¹⁰⁸ of all LGIT haemorrhage, representing significant morbidity and mortality, with 3% of patients with diverticulosis experiencing “severe life-threatening” diverticular haemorrhage.¹⁰⁹ As described earlier, diverticula tend to develop in weak areas of the colon wall caused by perforation of the vasa recta. As the diverticulum develops, the vasa recta vessels are stretched outwards by the bulging mucosa and submucosa, leaving them susceptible to injury.¹¹⁰ The gradual erosion and rupture of these vessels is responsible for occult or massive haemorrhages respectively. Both occult and massive bleeding is more common in right-sided disease, due to the relative thinness of the ascending colon wall.¹¹¹ While diverticular bleeding is usually self-limiting, large volume and rapid blood loss is accompanied with high rates of mortality. Patients with comorbidities, particularly those affecting their ability to clot, such as

liver disease, are at increased risk of poor outcomes.¹⁰⁸ Also at higher risk of diverticular bleeding are patients using aspirin or NSAIDs, with an odds ratio of between 1.9 and 18.4.¹¹² Inflammation does not play a role in diverticular bleeding.¹¹³

Symptomatic Uncomplicated Diverticular Disease

The repeated recurrence of symptoms such as pain and altered bowel habit, in the absence of radiological evidence of inflammation, characterise symptomatic uncomplicated diverticular disease (SUDD).¹¹⁴ The pathogenesis of SUDD remains controversial; there is some evidence that it involves a chronic low-grade inflammation, forming part of the diverticulitis spectrum,¹¹⁵ while others hypothesise that the term relates to patients with coexisting diverticulosis and functional disorder.¹¹⁶ This debate, however, is outside the scope of this review.

Diverticulitis

Diverticulitis describes the spectrum of diverticular disease that extends from subclinical peridiverticular inflammation to generalised peritonitis. It is associated with microscopic or macroscopic perforations of the colonic mucosa.

Diverticulitis appears to be responsible for an increasingly large burden of disease; studies based on inpatient admission data in the US, UK and Canada demonstrate increasing incidence of diverticulitis episodes requiring inpatient treatment.¹¹⁷⁻¹¹⁹ A study of the US nationwide inpatient sample database saw a reported 9.5% increase in number of admissions with a diagnosis of diverticulitis during the study period of 2002-2007.¹¹⁹ These results correlate with those of the Canadian study, which found that the rate of hospitalisations per 100,000 population rose from 94 in 1988, to 105 in 2001, representing an 11.7% increase in admission requirement.¹¹⁹

The true rate of complications arising from diverticulosis, however, is contentious. Traditionally the figure of 10-25% is used to describe the lifetime risk of a patient with diverticulosis, developing diverticulitis. This figure is derived from a large case study, which involved 47,000 radiologic examinations of the disease.⁷⁹ Use of the results of the study in this way has recently been called into question because the scans were of patients who required radiological evaluation, and were therefore more likely to be experiencing symptoms, and thus more likely to have underlying diverticulitis, rather than asymptomatic diverticulosis. Diverticulitis is still considered a common complication of diverticular disease; a retrospective study of 2222 patients identified as having diverticulosis on colonoscopy found that in an 11 year follow-up period between 23 and 95 patients developed diverticulitis, depending on the definition of diverticulitis applied.¹²⁰ This equates to a risk of developing the complication of 1-4.3% in an 11 year period. The same study found an increased risk of the development of diverticulitis in young patients identified as having diverticulosis on colonoscopy.

In terms of absolute risk of developing acute diverticulitis across all ages, there is a slight female predominance.¹²¹ This increased risk, however, only develops after menopause, with disproportionately more men in the group of patients under 40 years of age with acute diverticulitis.¹²²

Diverticulitis Diagnosis

The clinical triad of lower left-sided abdominal pain, fever and leucocytosis, in combination with changing bowel habit and raised acute inflammatory markers (CRP), has traditionally been used to identify patients with diverticulitis. When positive, these parameters appear to be highly specific for diverticulitis: 96-98%.¹²³ However, this clinical evaluation method is not sensitive, on average failing to identify 34% of diverticulitis presentations

correctly.¹²³ This is one of the reasons radiological imaging techniques play a large role in modern day diverticulitis management. As an imaging modality, ultrasound (US) is non-invasive, non-ionising and readily available. In the context of diverticulitis, it has acceptable sensitivity and specificity, both 90%. This is, however, dependant on the skill of the technician and clinician involved and is not commonly used in Australia. The development and increasing availability of CT technology, in combination with advancement in interventional CT-guided techniques, has meant US and contrast enema have been largely superseded in this area. With intravenous and intrarectal contrast, CT scans have a sensitivity and specificity approaching 100%¹²⁴ when considered in terms of the Ambrosetti CT findings: localised sigmoid wall thickening (<5mm), pericolic fat stranding, abscess extraluminal air and extraluminal contrast.¹²⁵ CT is also able to identify distant abscess formation and used to guide percutaneous abscess drainage. The role for magnetic resonance imaging (MRI) in diverticulitis has not been fully elucidated; one study found MRI to be equally as accurate as CT in the diagnosis of diverticulitis.¹²⁶ However, these results have not been replicated.¹²⁴ It has also been postulated that MRI could provide a “virtual colonoscopy”, reducing the need for the invasive procedure to investigate fistulae¹²⁴, but the high cost and limited availability of MRI technology may limit this utilisation.

Diverticulitis classification

A number of different classification systems are used, both clinically and in the scientific literature, to identify and characterise diverticulitis. This has led to the presence of conflicting terminology in academic writing, making it difficult to compare studies and synthesise research materials.¹²⁴

Traditionally, the Hinchey system, developed in 1978 by Hinchey et al. and based on clinical and surgical findings, is used to classify acute diverticulitis.¹²⁷ It has been modified a number of times to include clinical and

the vastly greater depth of information provided by the development of the CT scan as the primary imaging modality for diagnosis of diverticulitis (table 2A).

Table 2A: Modified Hinchey classification^{128 124}

Stage 0	Mild clinical diverticulitis
Stage 1a	Phlegmon or confined pericolic inflammation
Stage 1B	Pericolic or mesocolic abscess
Stage 2	Distant abscess (pelvic, intraabdominal or retroperitoneal)
Stage 3	Generalised purulent peritonitis
Stage 4	Faecal peritonitis

While this widely used classification system provides a platform for objective and consistent diagnosis, severity staging, and comparison within the scientific literature, it does not encompass the full spectrum of diverticular disease. Other classification systems involving descriptions of asymptomatic disease, symptomatic uncomplicated disease, and recurrent disease, have been produced to fill this apparent deficit.¹²⁹⁻¹³¹ These classifications, particularly the Hansen Stock system, are used throughout Europe, dominating the European scientific literature.¹²⁴

Table 2B: Hansen Stock Classification¹³⁰

Stage 0	Diverticulosis
Stage 1	Acute complicated diverticulitis
Stage 2	Acute complicated diverticulitis a) Phlegmon, peridiverticulitis b) Abscess, sealed perforation c) Free perforation
Stage 3	Chronic recurrent diverticulitis

The system of Ambrosetti et al., which categorises diverticulitis as either moderate or severe, was developed as a tool for clinicians. It focuses on using the increased quantity and detail of information provided by a CT scan to guide clinical decision-making.

Table 2C: Ambrosetti Classification of Diverticulitis¹²⁵

Moderate disease	Localised colonic wall thickening Pericolic fat stranding
Severe disease	Local or distant abscess formation Extraluminal air Extraluminal contrast

The Ambrosetti classification appears to allow for the most objective classification of diverticulitis using CT scans in isolation. For this reason, it is appropriate to use the Ambrosetti system for academic purposes.

Diverticulitis pathophysiology

There is growing evidence that the pathogenesis of diverticulitis is primarily based in deregulation of the inflammatory response, similarly to that of an inflammatory bowel disease. It seems that diverticular disease forms a spectrum of increasing inflammation ranging from a very low grade of

chronic inflammation in asymptomatic diverticulosis, which is increased in SUDD and highest in the acute flairs, which present as diverticulitis.

The spectrum is demonstrated by the density of lymphocytes, a group of cells involved in the inflammatory response, found in the colonic mucosa across the range of severities of diverticular disease. Patients with asymptomatic diverticulosis have been found to have a median lymphocytic density score of 6.5, which when compared to the density seen in healthy controls, 4, suggests a level of low grade inflammation in the bowel wall. The lymphocytic infiltration is again greater in SUDD, median 7, and highest in acute diverticulitis, median 11.¹³²

The inflammatory cytokine TNF- α is also seen in increased levels in diverticular disease and appears to play a role in the pathogenesis of diverticulitis. TNF- α levels in the colonic mucosal tissue increase with diverticular disease severity.²³ They are highest in acute diverticulitis, but also show a statistically significant increase in SUDD, when compared to mucosa of healthy individuals. TNF- α levels are not elevated in asymptomatic diverticulosis.¹³³ This supports the theory that diverticulosis, SUDD and acute diverticulitis form a spectrum characterised by increasing inflammatory activity.

When considering diverticular disease in the context of traditional inflammatory bowel diseases, mucosal TNF- α expression is in fact higher in acute diverticulitis than in Crohn's disease.¹³⁴ The study that identified this relationship also found overexpression of basic fibroblastic growth factor and syndecan 1 in diverticulitis, both of which are associated with acute exacerbations of Crohn's disease.

Gut Microbiota

It has been postulated that altered bowel microflora play a role in the development of diverticulitis. Animal models suggest that down regulation of normal microbiota, such as those from the *Bacteroidetes* group, creates an environment in which toxic bacteria predominate, impairing the barrier function of the colonic mucosa, and causing increased local expression of inflammatory cytokines.³⁶ Randomised control studies have also described increased remission rates in patients who take various probiotic formulas following acute diverticulitis episodes, suggesting a protective effect of increased populations of normal colonic microflora.^{135, 136} This has been supported by a recent, significant study in patients with diverticular disease, which demonstrated decreased *Akkermansia* populations in sections of bowel dense in macrophages, compared to sections of bowel which had a lower proportion of macrophages.¹³⁷

Obesity

Obesity has been established as a risk factor for developing diverticular disease. The Health Professionals Follow-up Study, referred to above, found a risk ratio of 1.79 for obese men (defined as a BMI>30) developing diverticulitis, when compared to lean men.¹³⁸ The role obesity plays in the pathogenesis of the inflammation that defines diverticulitis, however, has not been fully elucidated. It is likely that a combination of diet, altered bowel flora and chronic low-grade inflammation seen in obese individuals is involved in the biological mechanisms leading to the peridiverticular inflammation and microperforation that characterise diverticulitis.

Type 2 Diabetes Mellitus

T2DM, which, similarly to abdominal obesity, forms part of the metabolic syndrome¹³⁹ may also contribute to the development of diverticulitis. As discussed earlier (1.2.6), the epidemiological evidence regarding the

relationship diverticulosis and T2DM is conflicting. There is very little research that looks at the association between complications of diverticular disease, patient outcomes and T2DM. The study by Cologne et al. found that patients who present with complicated diverticular disease, and who have a comorbid diagnosis of T2DM, present in more severe disease states. They found that 12.2% patients with T2DM present with Hinchey stage 3 and 4 disease, in comparison with the 9.2% of patients without T2DM.¹⁴⁰ In particular, presentation with abscess, fistula or peritonitis appears to be more common in patients with T2DM. The same study identified a significantly increased length of stay and incidence of in-hospital infections in patients presenting with complicated diverticular disease in combination with T2DM.

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These studies, however, were not able to distinguish the proportion of these complications were attributable to T2DM as a causative factor, rather than T2DM as a co-morbidity, contributing to a patient who at baseline, is 'sicker', and more likely to have other conditions such as IHD and congestive cardiac failure (CCF), and less able to cope with an insult such as diverticulitis. More work is required in this area to confirm these findings and to further develop the understanding of the role DM plays in diverticular disease complications.

Body composition and Diverticular Disease

The association between body composition and diverticular disease has not been well studied. As discussed earlier, the positive correlations between obesity and risk of diverticulosis and risk of diverticulitis have been well established. The role of visceral adipose tissue in the disease, however, has not been fully defined. In a small (n=140) Korean study researchers demonstrated an association between increased levels of visceral adipose tissue and risk of diverticulosis.¹⁴¹ The same Korean group also demonstrated an increased risk of complicated diverticulitis in patients with higher levels of

visceral adipose tissue (VAT), again in a small study (n=133).¹⁴² These results have not yet been replicated in other populations. As discussed earlier, diverticular disease behaves differently in Asian patients,¹⁴³ so validation of these results in different ethnic groups is required before conclusions regarding the role visceral adipose tissue plays in the disease can be made. The association between skeletal muscle mass and diverticular disease has not yet been studied.

2.3 Pancreatic Malignancy

The pancreas is a heterocrine gland essential for glucose homeostasis and the digestion of carbohydrates and protein. The exocrine tissue is arranged into functional units of cell clusters surrounding microscopic ducts, which are called acini. These ducts connect to larger ducts which open into the main pancreatic duct, which joins the common bile duct to drain into the duodenum (the most proximal section of the small bowel). This ductal system is responsible for transporting the three enzymes: amylase, lipase and a variety of proteases, produced by the acinar cells, which are critical for digestion.¹⁴⁴

The endocrine cells are organised in clusters called islets of Langerhans, which are scattered throughout the exocrine tissue. Islets of Langerhans are comprised of alpha, beta, gamma and delta cells, which produce glucagon, insulin, pancreatic polypeptide and somatostatin respectively.¹⁴⁴

The diverse cell types that make up the pancreas make it susceptible to a number of diverse cancer types. This study will first discuss the most common type, PDAC,¹⁴⁵ and then go on to discuss pancreatic neuroendocrine tumours PNET.

Pancreatic Ductal Adenocarcinoma

PDAC is a common cancer with an Australian population incidence of 11 in 100,000, ranking as the 11th most commonly diagnosed cancer.¹⁴⁶ In contrast to the general trend towards reduced incidence of cancers, the incidence of pancreatic cancer is increasing.¹⁴⁷ Due to its poor survival rate, pancreatic cancer ranks much higher, 5th in Australia, in terms of cancer deaths.¹⁴⁶ Worldwide, the mortality rate of pancreatic cancer is 96%.¹⁴⁸ This poor prognosis is contributed to by a number of features that are unique to pancreatic cancer. The first is the anatomical location of the pancreas. It is a predominantly retroperitoneal organ that lies deep within the abdomen. This allows cancers to develop without detection until they have advanced to invading local structures, such as the major mesenteric vessels, or metastasised to peritoneal cavity or distant organs.¹⁴⁹ The second is the dense desmoplasia which characterises the tumour, producing a systemic inflammatory response and providing an environment for the cancer cells which results in lower tumour tissue concentrations of chemotherapy.¹⁵⁰

Pathophysiology

PDAC arises from the ductal epithelium. It can occur anywhere in the gland, but is most common in the head. The pathway from healthy pancreatic epithelial tissue to PDAC is not as well described as in other cancers, such as colon cancer, where the genetic progression from precursor adenomatous polyp to carcinoma has been demonstrated.¹⁵¹ Current research suggests that PDAC arises from a precursor lesion. Pancreatic intraepithelial neoplasia (PanIN) is the most common of these lesions, followed by intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs).¹⁵²

PanIN is often seen in the area adjacent to PDAC during surgical resection,¹⁵³ and has been classified histologically based on increasing cellular atypia from PanIN-1 to PanIN-3.¹⁵⁴ However, due to the relative difficulty in obtaining biopsies of the pancreas compared to organs such as the bowel and skin, a histological timeline for PDAC has not been fully established.¹⁵⁵ Mutation in the gene c-KRAS which encodes the protein KRAS is almost universal in human PDAC, present in >90% of PDAC cases,¹⁵⁶ as well as in 90% of precursor PanIN lesions.¹⁵⁷ KRAS appears to play a central role in driving the proliferation of cancerous cells in the hypo vascular and hypoxic environment that describes pancreatic cancer, by altering glucose metabolism and utilisation.¹⁵⁸ Other genetic mutations in tumour suppressor genes, most commonly CDKN2A, p53 and SMAD-4 occur with increasing frequency later in the progression from PanIN-2 to PDAC.¹⁵⁴

Immunomodulation

The immune system is critical in preventing tumour genesis by identifying and destroying mutated cells. In order to proliferate and grow, cancers must find ways to evade this immune response. In pancreatic cancer, >90% of the tumour mass consists of immune cells. Of these immune cells, there is a relative abundance of immunosuppressive cells, particularly regulatory T-cells, tumour associated macrophages and myeloid derived suppressor cells. These immunosuppressant cells allow the tumour to evade the body's cytotoxic T-cell anti-tumour response.¹⁵⁹

Inflammation

Inflammation is central to the pathophysiology of pancreatic cancer, functioning both as a risk factor for tumour genesis and progression, as well as consequence of the cancer.¹⁶⁰ The association between inflammation and PDAC was first established epidemiologically; pancreatic cancer is strongly positively associated with chronic pancreatitis.¹⁶¹

A number of studies have sought to define the relationship between inflammation and PDAC by inducing or inhibiting inflammation.¹⁶⁰ The key findings of this series of experiments was that in KRAS mutated mice PDAC pathogenesis does not occur until the induction of chronic pancreatitis,^{162, 163} and that anti-inflammatory treatment with cyclooxygenase (COX) inhibitors prevents progression from PanIN precursor lesions to PDAC.¹⁶⁴

Desmoplasia

Pancreatic cancer is characterised by extensive desmoplasia surrounding cancer cells.¹⁶⁵ Desmoplasia describes the deregulated proliferation of myofibroblasts and production of extracellular matrix, resulting in the rapid formation of dense fibrous tissue.^{166, 167} The extent of the desmoplastic reaction is associated with poor outcome; patients with higher levels of fibroblast proliferation have shorter survival times than patients with lower levels.^{168, 169} This is consistent by the work by Kadaba et al, who demonstrated that progressive accumulation of stromal cells results in a “pro-survival and pro-invasive effect on tumour cells”.¹⁷⁰ These poor outcomes can, at least in some part, be explained by obstruction of chemotherapy delivery caused by the low vascularity and high interstitial pressures of the desmoplastic environment.¹⁷¹

Pancreatic Stellate Cells

There is increasing interest in the role that pancreatic stellate cells (PaSC) play in the formation of the unique desmoplastic stroma of pancreatic cancer.

In physiologic conditions PaSCs exist in a dormant or quiescent state, containing vitamin A droplets and producing only very low levels of extracellular matrix proteins, cytokines and growth factors, and with similarly low levels of cell proliferation.¹⁷² Under normal physiological conditions PaSCs are also able to produce metalloproteinases (MMPS), enzymes which

breakdown extracellular matrix proteins, as well as inhibitors of these enzymes, tissue inhibitors of metalloproteinases (TIMPS).¹⁵⁰ Based on their ability to produce these factors, it is thought that PaSC play a key role in the maintenance of pancreatic architecture.

In contrast, pathological states are associated with high concentrations of activated PaSCs, triggering them to function as myofibroblasts. PaSCs have been shown to be responsible for producing the desmoplasia that characterises PDAC.¹⁷³

In terms of the role of PaSCs in PDAC, the extracellular matrix produced by these cells lays down a kind of framework to support the growth of the cancerous epithelial tissue. In mouse models of PDAC, the addition of human PSCs resulted in accelerated growth of tumours, as well as increased risk of regional and distant metastasis.¹⁷⁴

Risk Factors

Genetic

There is clear evidence that genetic factors are, at least in part, responsible for the development of some PDACs. First-degree relatives of patients with pancreatic cancer are at a significantly higher risk of developing the condition themselves, when compared to the general population. This risk is again much higher in individuals who have three or more relatives with the condition, with one study estimating their chance of developing the condition to be 57 times that of the general population.¹⁷⁵ A number of hereditary syndromes involving well described genetic mutations account for a small portion of PDACs.¹⁷⁶ These include hereditary pancreatitis,¹⁷⁷ hereditary breast and ovarian cancer syndrome,¹⁷⁸ and Peutz-Jeghers syndrome.¹⁷⁹

Interestingly, blood group O is associated with a lower risk of PDAC than A, B and AB.¹⁸⁰

Pancreatitis

Chronic inflammation of the pancreas (pancreatitis) is the most significant risk factor for PDAC, with pancreatitis patients experiencing 14 times the risk of developing pancreatic cancer than the general population.¹⁶¹ There are two proposed mechanisms that implicate chronic pancreatitis in the development of PDAC. The first is that the inflammation and tissue damage characterising chronic pancreatitis creates an environment that accelerates PanIN and PDAC formation in mouse models of KRAS mutation.¹⁶² The other is that autophagy, a crucial intracellular degradation process that destroys unneeded or dysfunctional cellular components, is impaired in pancreatitis.¹⁸¹

Diabetes mellitus

An association between diabetes mellitus and an increased risk of developing PDAC has consistently been demonstrated by large population-based studies. A recent meta-analysis suggests that while this association is certainly present, it seems to have been over estimated in the early studies of the 1980s and 1990s.¹⁸² Disentangling cause and effect relationships in this area has been difficult. The ability of PDAC to induce diabetes has been demonstrated in both animal models,¹⁸³ as well as suggested by human studies.^{184, 185} However, the finding that chronic diabetes (duration >5 years) is associated with PDAC, supports the suggestion that diabetes is a risk factor for the disease, because due to the aggressive nature of PDAC, it is unlikely that a PDAC, causing the increased incidence of diabetes, could go undiagnosed for this long period of time.¹⁸⁶

Environmental

Environment appears to play a significant role in the development of pancreatic cancer with a number of risk factors identified. Obesity, particularly abdominal obesity, is associated with an increased risk of PDAC.¹⁸⁷ Cigarette smoking and heavy alcohol consumption also increase the risk of pancreatic cancer.¹⁸⁸ The relationship between consumption of coffee and risk of developing pancreatic cancer has been assessed by a number of studies, with conflicting results.¹⁸⁹ The current global consensus is that consumption of coffee does not increase the risk of developing pancreatic cancer.¹⁹⁰

Prognosis

As discussed earlier, PDAC carries a particularly poor prognosis. When patients diagnosed at all tumour stages of PDAC are considered together, the 5-year survival rate is 7%. This figure encompasses the 9% of PDAC patients who are diagnosed early, with a tumour that is completely within the pancreas, and which has not spread to lymph nodes or metastasised to distant organs (stage 1). These patients with stage 1 disease have a 5-year survival rate of 27%. It also encompasses the 57% of patients at the other end of the spectrum, who present with advanced disease, which has metastasised to distant organs (stage 4). This stage 4 disease group has a 5-year survival rate of 2%.¹⁹¹

Management

The management of PDAC is largely dependent on two factors: the extent of the disease and the wellness of the patient. Currently there are three broad groups of therapies available: surgery, radiation therapy and chemotherapy, which are used in isolation or in combination.

Surgical

Radical surgical resection is required for the possibility of long-term survival in patients with PDAC. However, it is only attempted on three conditions: firstly that the tumour has not infiltrated critical local structures (locally advanced), secondly that there is no metastatic disease, and thirdly that the patient is well enough to survive what is a highly invasive procedure. In PDAC patients who have a resection, the 5-year survival rate is still only 24%.¹⁹² For head of pancreas tumours a Whipple's procedure, or pancreatoduodenectomy, is performed. This involves removing the head of the pancreas, the gall bladder and distal biliary tree, and the most proximal part of the small bowel, the duodenum. In some cases (classic Whipple's) the distal part of the stomach and the pylorus is also removed. A recent Cochrane review found no "relevant differences in mortality, morbidity and survival" between the classic Whipple's surgery and the pylorus preserving surgery, based on current available evidence.¹⁹³ For pancreatic body and tail tumours a distal pancreatectomy is performed. Occasionally a total pancreatectomy is required based on tumour location and extent of local tissue invasion.¹⁴⁹

Radiation therapy

Radiation therapy has been used in PDAC both in the neoadjuvant setting, after definitive resection and as a palliative treatment for locally advanced disease. While metastatic disease burden is a significant cause of morbidity and mortality, 30% of PDAC patients die as a result of destruction of local pancreatic and surrounding structures.¹⁹⁴ This suggests a role for radiation therapy in the local control of PDAC. However, the actual benefit of radiation therapy in practice remains contentious. Traditionally the proximity to other gastrointestinal tract structures, which tolerate radiation poorly, has limited the dose that can be delivered to pancreatic tumours.¹⁹⁵ The consequence of this, reduced efficacy, was evident in the large phase 3 LAP07 trial, which

showed no additional benefit of the addition of radiation therapy to chemotherapy, in locally advanced PDAC.¹⁹⁶

Stereotactic radiation therapy delivers high doses of radiation to a more focused area than traditional radiation therapy, resulting in less damage to surrounding tissues.¹⁹⁷ A recent systematic review of 19 clinical trials assessing the clinical utility of stereotactic radiation therapy demonstrated both local control and survival benefits in patients receiving this therapy. However this systematic review only included a total of 1009 patients, from non-randomised trials. Particularly in light of the recent large randomised trials, which demonstrated no benefit from traditional radiation therapy, further randomised control trials are required to determine the effectiveness of stereotactic radiation therapy in PDAC.¹⁹⁸

Medical

Given the high proportion of patients who present with either locally advanced or metastatic PDAC, medical therapy is the mainstay of treatment. However, a lack of effective systemic treatment options contributes to the poor prognosis of PDAC.¹⁹⁹

As discussed by Segelov et al in their recent, comprehensive review of the current management of PDAC, 5-fluorouracil (5-FU) and gemcitabine form the foundation of modern PDAC chemotherapy regimens. 5-FU is an analogue of uracil, which prevents tumour growth by disrupting RNA synthesis.²⁰⁰ Gemcitabine is a nucleoside agonist that targets deoxyribonucleic acid (DNA) replication to induce tumour cell apoptosis. Both 5-FU and gemcitabine are used as monotherapies in PDAC. Often this is in the adjuvant setting, where there does not appear to be a survival benefit associated with either drug over the other, however gemcitabine displays a favourable side effect profile.²⁰¹

Otherwise, these monotherapies are used in patients deemed unable to tolerate the combination chemotherapy regimens, often due to old age or comorbidity burden.¹⁹⁹

The development of two key combination chemotherapeutic regimens has modestly improved the prognosis of PDAC. The first of these is FOLFIRINOX, which is a multi drug therapy comprised of fluorouracil, irinotecan, oxaliplatin, and leucovorin.²⁰² It showed improved survival over gemcitabine monotherapy, the previous gold standard treatment, and produced a 48% one year survival rate in patients with metastatic disease.²⁰³ FOLFIRINOX has also been shown to be a successful neo-adjuvant therapy in borderline resectable disease,²⁰⁴ as well as demonstrating promising response rates in locally advanced PDAC.²⁰⁵ The second is concurrent treatment with gemcitabine and nab-paclitaxel (albumin bound paclitaxel), which is a microtubule stabiliser that induces apoptosis in mitotic cells.²⁰⁶ The gemcitabine nab-paclitaxel dual therapy was again trialled against gemcitabine alone, producing a 35% one year survival rate in patients with metastatic disease.²⁰⁷ There has been little study of the gemcitabine nab-paclitaxel regimen in locally advanced PDAC.

Both FOLFIRINOX and gemcitabine and nab paclitaxel regimes are associated with chemotherapy toxicity. Adverse events associated with chemotherapy are often defined in the academic literature using the National Cancer Institute Common Toxicity Criteria Adverse Events manual v4.0, with grade three, four and five adverse events described as 'toxicity'. The adverse events most significant in patients on the FOLFIRINOX regimen are: diarrhoea, peripheral neuropathy, thrombocytopenia and neutropenia.²⁰⁸ Neutropenia is particularly significant in FOLFIRINOX treatment affecting 45.7% of patients.²⁰³ A number of groups have suggested modifications to the FOLFIRINOX regimen, often involving removing the 5-FU bolus, to improve

tolerability.²⁰⁹⁻²¹¹ Their studies demonstrated a reduction particularly in haematological toxicities. However, while these studies suggest that efficacy is maintained, these regimens compared to the have not been robustly compared to the full FOLFIRINOX regimen in large randomised control trials.

In the phase 3 study comparing gemcitabine alone to the gemcitabine nab-paclitaxel regimen, adverse events most significant in patients taking a combination gemcitabine and nab paclitaxel were grouped as haematological, non haematological and neurological.²⁰⁶ Neutropenia was the most common haematological toxicity with 38% of patients experiencing grade three or higher neutropenia, and 3% experiencing an episode of febrile neutropenia. In the non-haematological category significant fatigue and diarrhoea were both common, effecting 17% and 6% of patients on gemcitabine nab-paclitaxel respectively. Finally, peripheral neuropathy is particularly significant in this patient group, with 17% of patients experiencing grade 3 or above peripheral neuropathy, which is often irreversible. Peripheral neuropathy is more common later in Gem-Nab-P treatment, with a median time of onset of 140 days.²⁰⁶ While this data provides rigorously collected data surrounding toxicities significant in patients taking gemcitabine nab-paclitaxel, it is important to recognise that often data collected in these trials is not perfectly reflected in practice, often due in part to differences in patient selection for a clinical trial versus those who receive drug as standard clinical care.

Neuroendocrine Tumours

PNET arise from pancreatic islet cells, and are much less common than PDAC accounting for between 2 and 5% of all pancreatic malignancies. This equates to a clinical population incidence of approximately 2 per 1,000,000;²¹² however, Grimelius et al demonstrated an incidence of 1.5% on autopsy.²¹³ This high proportion of undiagnosed PNETs, speaks to the indolent course of the majority of these tumours. The rarity of the diagnosis of NF-PNET

compared to other malignancies, combined with its usually benign course, has resulted in a relatively limited body of surrounding literature.

Of diagnosed PNETs, 85% are non-functioning (NF-PNET). This describes tumours that do not produce distinct clinical syndromes through hormone secretion.²¹⁴ With the improvement in quality, and increase in frequency of cross-sectional imaging, the diagnosis of NF-PNETs, particularly as incidental findings,²¹⁵ is becoming more common.^{216, 217}

Functioning PNETs are beyond the scope of the research presented in this thesis, so will not be discussed in this review.

Pathogenesis

Similarly to PDAC, the majority of PNETs are caused by sporadic mutations. The mutations that are seen in PNETs are different to those common in PDAC: KRAS, CDKN2, SMAD-4 and TP53. Instead, mutations of MEN1, DAXX/ATRX and mTOR are most common in PNET.²¹⁸ It is important to note that this mutation of the MEN1 gene is specific to the PNET cells, rather than the global mutation that describes multiple neuroendocrine type 1 (MEN1) syndrome.²¹⁹

The cause of the sporadic mutations that lead to PNET is unclear; as in other cancers, it is likely a multifactorial process involving a genetic predisposition precipitated by environmental triggers. Old age is the most significant risk factor, with the majority of PNET diagnoses occurring in the 8th decade of life.²²⁰ Similarly to PDAC, obesity and smoking are more common in patient populations with PNET, than the general community.²²¹

While most PNETs occur as a result of sporadic mutation, a proportion can be attributed to one of four described inherited syndromes. The most common of these is MEN 1 syndrome, followed by von Hippel-Lindau disease.

Neurofibromatosis type one (von Recklinghausen's disease) and tuberous sclerosis are less common syndromes associated with PNET.²²²

Diagnosis

Diagnosis of PNET is made using a combination of anatomical imaging, functional imaging and immunohistochemistry.²²³ Anatomical imaging is often the modality with which a pancreatic lesion is identified, and can later be used to monitor tumour growth. Functional imaging is recommended for all patients at the diagnosis of PNET. The gold standard modality is ⁶⁸GA (DOTOTATE), which provides the highest spatial resolution, and image quality.²²⁴ Immunohistochemistry, specifically chromogranin A, synaptophysin and Ki67, are used to diagnose and provide proliferation activity information.²²⁵

Management

Treatment of PNET is difficult and varied, ranging from expectant management, to surgery and systemic radionuclide or chemotherapy.

Decisions are based on the size of the tumour, the metastatic status of the disease and the functional and co-morbid state of the patient.

Surgical resection is the main stay of curative management for PNET.

Tumours of ≤ 2 cm are unlikely to progress or metastasise and so are managed expectantly.²²⁶ If tumours display aggressive features such as Ki 67 $> 2\%$ (Ki 67 is a marker of cellular proliferation), rapid growth, dilation of the pancreatic duct or lymph nodes suspicious for metastatic disease, surgery is indicated.²¹⁷

The surgical options are the same as those described for PDAC, however, given its less aggressive nature occasionally enucleation or middle

pancreatectomy are considered to preserve endocrine and exocrine functions of the pancreas.²²⁷

In PNET, medical therapy is usually given instead of surgical resection, rather than as an adjunct to.²²³ Both traditional cytotoxic chemotherapies, and the targeted therapies everolimus (mTOR inhibitor)²²⁸ and sunitinib (tyrosine kinase inhibitor)²²⁹ have showed tumour response and survival benefits in large clinical trials, in advanced PNET.

Prognosis

Metastatic disease at diagnosis carries a significantly worse prognosis than localised disease (40% 5 year survival rate compared to 93%). Tumours that are symptomatic at diagnosis (manifesting as pain, jaundice, anorexia, or weight loss) are also associated with poor prognosis asymptomatic disease. And finally high cellular proliferation as marked by high Ki67 percentage, and large tumour size at diagnosis are also associated with poor prognosis.²³⁰

Body composition in pancreatic malignancy

Cachexia is characteristic of PDAC and advanced PNET.^{231, 232} The pathophysiology of muscle wasting has been described in depth earlier in this review (section 2.1), but there are some factors that apply particularly to pancreatic malignancies. The first is that malnutrition is common in this patient group. Malnutrition is complex, and multifactorial syndrome. Anxiety surrounding poor prognosis, abdominal pain, fatigue, duodenal stenosis, pancreatic exocrine insufficiency, malabsorption and constipation, have been identified as significant, independent contributors to malnutrition in pancreatic cancer patients.²³³⁻²³⁵ Secondly, as has been discussed earlier (sections 2.1 and 2.2), PDAC is a highly inflammatory tumour, which is a key driver of muscle wasting.⁶³ And thirdly, due to its aggressive nature, the rapid

growth and energy requirement of PDAC and its surrounding desmoplasia, drives a hypercatabolic state in the body.²³⁶

Body composition and prognosis

A number of retrospective studies have identified low muscle mass at diagnosis, as well as a reduction in muscle mass during the course of disease, to be poor prognostic factors in PDAC.²³⁷⁻²⁴⁰ Myosteatorsis, however, has not been so well investigated in pancreatic cancer. An association between myosteatorsis and poorer prognosis in pancreatic cancer was recently demonstrated by Lobo et al.²⁴¹ The retrospective design of their study, however, has been criticised for its inability to include muscle function in analysis²⁴² and so requires prospective replication. There is no current published literature describing body composition phenotypes in PNET.

Body Composition and chemotherapy pharmacokinetics

There is growing evidence that myopenic patients experience a higher rate of adverse events associated with chemotherapy than patients who are not myopenic, across a wide range of cancers and regimens.²⁴³⁻²⁴⁶ The reason for this susceptibility to toxicity has not been fully described. It is feasible that this can in part be attributed to variations in volume of distribution, within any given BSA as a result of variation in body composition parameters.

BSA calculated using the Mosteller formula [$BSA (m^2) = (\text{height (cm)} \times \text{weight (kg)})/3600$], is used to dose routine cytotoxic chemotherapy.²⁴⁷ Similarly to BMI, BSA cannot discriminate between body composition parameters; a patient who is obese, but myopenic, may share the same BSA as a patient of the same height with a large volume of skeletal muscle, and much less adipose tissue.²⁴⁸ Dependent on the extent to which a drug is hydrophilic or hydrophobic, it distributes within muscle and adipose tissue differently, creating body composition specific volumes of distribution.²⁴⁹

Prado *et al.* first investigated this concept in chemotherapy in 2007. Their study demonstrated that a higher 5-fluorouracil dose/kg of lean body mass was associated with increased dose limiting toxicity.²⁵⁰ Since this study there has been little published in the scientific literature.²⁴⁸ Notably, there has been no work examining the relationship between dose to lean body mass ratio and toxicity in the characteristically myopenic pancreatic cancer patient group, or in gemcitabine based regimens.

Conclusion

The relationship between body composition, inflammation and disease has been the subject of much scientific investigation. However, there remains much that is incompletely understood. Following is a body of work studying the area of body composition in surgical disease of the gastrointestinal tract. It focuses on two conditions: diverticular disease and pancreatic malignancy. Each chapter seeks to contribute evidence towards the understanding of the underlying intra-abdominal pathology and its relationship with body composition, as well as to provide suggestions in regards to how this understanding could be exploited by clinicians to better manage patients with diverticular disease and pancreatic malignancies.

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Chapter 3: Body composition in diverticular disease

3.1 The role of body composition in diverticular disease

Introduction

Diverticular disease is common and increasing in prevalence. Its complications constitute a significant disease burden, both in terms of morbidity and mortality. Despite the significant body of recent research surrounding diverticular disease and its complications, the pathogenesis is not fully understood.

Obesity, as defined by increased BMI, increases an individual's risk of developing the inflammatory complication of diverticular disease. This may be due, at least in part, to the chronic, sub-clinical inflammatory environment that is produced by excess visceral adipose tissue. This is the same inflammation that has been implicated in other features of the metabolic syndrome, particularly T2DM. Greater understanding of the role of visceral adipose tissue levels in the pathogenesis of diverticular disease will allow for the development of more effective preventative strategies and also may provide better targeted treatment regimes

While BMI gives some indication of the amount of visceral adipose tissue an individual is carrying, due to differences in skeletal muscle and sub-cutaneous adipose tissue volumes in the population, VFA can be measured with significantly increased accuracy using single slice CT techniques. A small study, of an ethnically homogenous Korean population has, using these

techniques shown a relationship between visceral fat and diverticular disease (see chapter 2.2). This work requires replication and validation in a different, larger cohort. Precise understanding of risk factors for diverticular disease and its serious complications will allow for more targeted research into the elusive pathogenesis of this spectrum of disease. It will also allow clinicians to provide more accurate, personalised advice surrounding prognosis and management of diverticular disease.

The following study was designed to study the role of body composition in diverticular disease in a large Australian population. It will also study the association between the metabolic syndrome and diverticular disease.

Body composition differences in diverticular disease

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Background

Diverticulosis describes the presence outwards 'sac-like' protrusions of the colonic wall. It is a common condition, of increasing incidence.²⁵¹

Diverticulosis can be complicated by diverticulitis; the macroscopic inflammation of a diverticulum or the peri-diverticular area.

The pathogenesis of diverticulosis and diverticulitis have not been fully elucidated. Mucosal wall thickening²⁵² and alterations in expression of colonic neurotransmitters²⁵³ are associated increased intraluminal pressures and appear to play a role in the development of diverticulosis. Inflammation plays a central role in diverticular disease, increasingly implicated both locally and systemically, from asymptomatic diverticulosis, to symptomatic uncomplicated diverticular disease, peaking with acute diverticulitis.²³ This dysregulation in inflammation appears to be associated with alterations in gut microbiome.²⁵⁴

Obesity is also associated with diverticular disease, particularly acute diverticulitis.¹³⁸ Similarly to diverticular disease, obesity is an inflammatory state. Visceral fat is the term used to describe adipose tissue within the abdominal cavity, surrounding the abdominal organs. The inflammatory cytokines tumour necrosis factor alpha (TNF- α) and interleukin 6 (IL-6) are produced by visceral adipose tissue and present in higher concentration is

obesity,²¹ creating a low-grade systemic inflammatory state, marked by increased levels of c-reactive protein (CRP).⁷

Extramyocellular fat (EMF) is a term used to describe the ectopic, visible deposition of adipose tissue between muscle bundles. Increased EMF levels are associated with both obesity (increased BMI), and increased VFA. Increased EMF levels also predict of insulin resistance, independently of BMI,^{41, 255} suggesting that extramyocellular fat plays a role in metabolism outside of its association with obesity. It is not clear, however, whether intermuscular fat has a causative relationship with insulin resistance, or it is acting as a marker for metabolic dysfunction.⁴³ The association between extramyocellular fat and diverticular disease has not been investigated.

A small study looked specifically at the relationship between diverticular disease and visceral adipose tissue in a Korean population, demonstrating a positive association between visceral fat area (VFA) and diverticulosis, but not diverticulitis.¹⁴¹ A more recent study demonstrated an association between visceral obesity and diverticulosis, even in patients with a normal BMI. It did not, however, assess incidence of complicated disease.²⁵⁶

This study aims to further characterise the relationship between body composition and diverticular disease in a racially heterogeneous Australian cohort. It also aims to investigate the relationship between the metabolic syndrome and diverticular disease.

Methods

Patients were identified using a search of the computed tomography (CT) database with the prefix 'divertic'. The inclusion criteria were: age greater

than 18 years, abdominal and pelvis CT scan between 2011-2014, with abdominal pain as the indication for CT scan. The exclusion criteria were: the presence of any small bowel diverticula, co-morbid inflammatory bowel disease or other intra-abdominal inflammatory pathology, malignancy, liver cirrhosis and end stage kidney disease (eGFR <30).

The diagnosis recorded in CT report grouped the patients into: acute diverticulitis, uncomplicated diverticulosis and control (no diverticulosis). A single radiologist reviewed all diverticulitis scans to confirm the presence of peridiverticular inflammation. Medical records were used to identify demographic and metabolic co-morbidity information.

Spinal level L3 CT DICOM (Digital Imaging and Communication in Medicine) images were used for body composition analysis. A single operator performed all analysis using SliceOmatic software v4.3 (TomoVision, Canada). Hounsfield unit (HU) threshold limits -29 to +150 were used to identify muscle, -190 to -30 to identify subcutaneous and extramyocellular fat and -150 to -50 to identify visceral adipose tissue.

Due to the non-parametric nature of the data, the Kruskal Wallis test was used to identify significance of difference between continuous variables and the chi square test was used to identify significance of relationship between binary variables. A p value <0.05 was considered significant in all analyses.

Results

Demographics

This study included 271 patients, of whom 83 were controls, 93 had diverticulosis and 95 had diverticulitis. There was no significant difference in age, sex or smoking status between the 3 disease groups. (table 1)

Body composition

There were significant differences in adipose tissue cross-sectional area between the three disease groups. Visceral fat area (VFA) was significantly higher in both the diverticulosis group (214.97cm²) and the diverticulitis group (203.23 cm²), than the control group (149.20 cm²) (p<0.001 and p<0.001). There was no difference in VFA between the diverticulosis and diverticulitis groups.

Similarly, visceral to subcutaneous fat area ratio (VFA:SCFA) was higher in the diverticulosis (0.82) and diverticulitis (0.74) groups than the control group (0.50), (p=0.019 and p=0.005, respectively). There was no difference in VFA:SCFA between the diverticulosis and diverticulitis groups.

The diverticulosis group had a significantly higher level of extramyocellular fat (EMCF) (8.42 cm²) than the control (6.55 cm²) and diverticulitis (6.79 cm²) groups. There was no difference in skeletal muscle area between the three groups.

Metabolic syndrome

There was no difference in prevalence of type 2 diabetes mellitus (T2DM) between the disease groups. Dyslipidaemia was more common in the diverticulosis group (48%) than both the control (29%) and diverticulitis (27%) groups (p=0.003 and p=0.006, respectively). Hypertension was also more common in the diverticulosis group than the control group (59% v 40%, p=0.008), but not the diverticulitis group (40%).

	Control (n=83)	Diverticulosis (n=93)	Diverticulitis (n=95)	p value
Age (years), Median (IQR)	56 (43-67)	63 (47-78)	60 (49-73)	0.07
Male, n (%)	37 (45)	47 (51)	46 (48)	0.77
Significant smoking history n=185 n, (%)	24 (45)	31 (50)	41 (59)	0.32
VFA (cm ²), Median (IQR)	149.20*+ (73.5-219.9)	214.97+^ (130.8-318.6)	203.23*^ (135.7-277.2)	<0.001 *<0.001 +<0.001 ^0.39
VFA:SCFA Median (IQR)	0.50*+ (0.35-0.91)	0.82+^ (0.46-1.34)	0.74*^ (0.50-1.01)	0.01 *0.005 +0.019 ^0.52
EMFA (cm ²), Median (IQR)	6.55*+ (2.33-12.31)	8.42+^ (4.85-13.70)	6.79*^ (2.82-12.56)	0.001 *0.55 +0.001 ^0.04
SkMA (cm ²), Median (IQR)	137.34 (115.1-166.7)	143.85 (116.3-172.3)	136.6 (106.2-168.0)	0.68
T2DM, n (%)	21 (26)	24 (27)	16 (17)	0.24
Dyslipidaemia , n (%)	23 (29)*+	43 (48)^+	26 (27)*^	0.004 *0.45 ^0.006 +0.003
Hypertension, n (%)	32 (40)*+	53 (59)+^	42 (44)*^	0.02 *0.77 ^0.05 +0.008

Table One: Body composition and metabolic syndrome in diverticular disease and controls

One-way analysis of variance was used to determine significance in relationship of characteristic and disease group (presented in bold). When significant, Kruskal-Wallis test was used. Chi-square test was used to test significance of relationship between categorical variables

Abbreviations: visceral fat area (VFA), subcutaneous fat area (SCFA), extramyocellular fat area (EMFA), skeletal muscle area (SkMA), type 2 diabetes mellitus (T2DM)

Discussion

In this study we have demonstrated key differences in both the distribution of adipose tissue and prevalence of the metabolic syndrome in diverticular disease.

There was a higher absolute level of visceral adipose tissue, as well as a higher proportion of visceral adipose tissue in relation to subcutaneous adipose tissue, in the diverticulosis and diverticulitis groups, when compared to control. While the finding that diverticulosis was associated with an increased level of visceral adipose tissue was congruous with the previous study in this area,¹⁴¹ our finding (n=266) that diverticulitis was also associated with increased visceral adipose tissue, when compared to a control group, was not shown in that smaller, ethnically homogeneous cohort (n=133).

Skeletal muscle area was not different between the groups. Due to the chronic inflammatory nature of diverticular disease, we anticipated a reduced median muscle area in the diverticular disease groups. It is possible the levels of chronic inflammation are insufficient to affect muscle.

While efforts were made to select appropriate patients for both the control and diverticulosis groups, by excluding patients with co-morbid conditions (other inflammatory disease, cirrhosis, renal failure), which may impact body composition, the patients in these groups were not entirely 'healthy' controls, as they had abdominal pain, significant to the extent that it warranted the radiation and cost associated with a CT scan. The retrospective nature of this study means that body composition phenotypes that increase the risk of diverticular disease can not be differentiated from body composition changes which result from the chronic inflammation associated with diverticular

disease. Future prospective research is required to better elucidate the relationship between body composition phenotype and diverticular disease.

In summary, we found patients with diverticulosis and diverticulitis had increased visceral fat and more features of the metabolic syndrome. Further longitudinal observational and interventional studies are required to determine whether these are modifiable factors that affect the disease course of diverticular disease.

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Conclusion

The association between body composition and diverticular disease has not been fully elucidated. Our work's consistency with previous work (see discussion) strengthens the evidence that increased visceral adipose tissue is associated with diverticular disease. Due to the retrospective nature of our study, and the others that have studied this area, we cannot comment on the cause-effect timeline. Further longitudinal research may achieve this. Given the high incidence of visceral obesity and diverticular disease, the comparatively low incidence of diverticulitis and the long lead-time, this would require large prospective cohort studies to address this question. An interventional study of the effect lifestyle modifications which reduce visceral adipose tissue, and their impact on SUDD and acute diverticulitis incidence, would better elucidate this relationship, in addition to investigating preventative strategies. While there were significant differences in prevalence between the proportion of patients with hypertension and dyslipidaemia between the diverticular disease and control groups, there was no difference in diabetes mellitus prevalence. Given the tendency for these conditions to cluster together, this is surprising, and warrants further research.

3.2 Metformin use in diverticular disease

Despite their shared risk factors (obesity, alcohol, physical inactivity – see chapter 2) we found that there was no difference in diabetes mellitus prevalence between the control and diverticulosis or diverticulitis groups. One explanation for this is that diabetes treatment mitigates the risk of diverticular disease, particularly diverticulitis, by reducing the degree of local, intra-abdominal inflammation. The following study presents the results of our investigation into the relationship between hypoglycaemic medication use and risk of acute diverticulitis, within the diabetic population.

REPORT



Metformin use in diabetics with diverticular disease is associated with reduced incidence of diverticulitis

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ABSTRACT

Background and aims: There is no current, evidence-based therapy to prevent acute diverticulitis in patients with diverticular disease. Metformin has been shown to have anti-inflammatory effects in a number of disease states, in both animal models and in human observational studies. The potential therapeutic efficacy of metformin in diverticular disease has not been investigated.

This study aims to describe the relationship between metformin use and diverticular disease in patients with diabetes mellitus.

Methods: This was a retrospective case-control study. It compared metformin and other hypoglycaemic medication use in diabetic patients with uncomplicated diverticulosis to those with acute diverticulitis. Patients were identified using hospital International Classification of Diseases 10 (ICD-10) data, and radiology, pathology and scanned medical record databases were used to confirm diagnoses and collect all information. Chi square tests were used to determine significance of difference in categorical variables, and Mann-Whitney tests were used for continuous data.

Results: There were 174 patients with uncomplicated diverticulosis and 175 patients with acute diverticulitis. A diagnosis of acute diverticulitis was associated with a significantly lower incidence of metformin use, than a diagnosis of uncomplicated diverticular disease (44% compared to 60%, respectively, $p = .002$). Other oral hypoglycaemic drugs and insulin were not associated with a lower incidence of diverticulitis ($p = .12$ and $p = .24$, respectively).

Conclusion: Metformin use is associated with reduced incidence of diverticulitis in diabetic patients with diverticular disease. The utility of metformin as a therapeutic agent to reduce the risk of diverticulitis in patients with diverticular disease warrants further randomised, prospective, interventional investigation.

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Introduction

Diverticulitis, the acute, inflammatory complication of diverticular disease, results in a large burden of disease and is increasing worldwide [1,2]. While this increase is multifactorial, it can certainly be, at least in part, attributed to the change in two of its risk factors, with a continuing rise in life expectancy [3] and in obesity [4]. Despite its growing prevalence, there has been little recent progress in the prevention of diverticulitis. There are currently no effective therapeutic options to reduce the risk of this serious inflammatory complication [5]. While the anti-inflammatory drug mesalamine showed promise in early investigator led clinical trials, [6] it ultimately failed to reduce diverticulitis recurrence in large phase-3 placebo-controlled clinical trials [7,8].

Metformin, an oral hypoglycaemic drug, has been used in the treatment of type-2 diabetes mellitus (T2DM) since the 1950s, to reduce hepatic glucose production and increase muscle insulin sensitivity. However, despite its long history of use, metformin's molecular mechanism of action has not been fully described. Recent animal and human studies

have suggested that metformin can play a modulating role in colonic pathological inflammation [9] and gut flora imbalance [10].

This study aims to define the relationship between metformin use and the incidence of acute diverticulitis, to assess the potential utility of metformin as a preventative agent against diverticulitis. This would be an off label use of metformin.

Methods

This was a retrospective cohort study of patients with both diabetes mellitus and diverticular disease. Patients were identified using an International Statistical Classification of Diseases and Related Health Problems 10 (ICD-10) coding search (K57 and E11 for diverticular disease and diabetes mellitus) of hospital records for admissions between 2009 and 2015. Inclusion criteria were: age >18 years, current diagnosis of diabetes and computed tomography (CT) evidence of colonic diverticula within the scanned medical record. A CT diagnosis was used because it is more accurate

than clinical diagnosis, ultrasound and endoscopy, with a sensitivity and specificity for diverticulitis approaching 100% [11]. There were no exclusion criteria.

A medical chart review was conducted to collect demographic information, hypoglycaemic medications taken at the time of admission, complications of disease episode (abscess and perforation) and biochemical markers of diabetic control. Renal impairment was defined as an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m², since this is the consensus level below which metformin is contraindicated [12].

The diagnoses of uncomplicated diverticulosis and acute diverticulitis were confirmed using the CT report.

Statistical analysis

IBM SPSS Statistical software (Armonk, NY) was used to conduct all analysis. Binary and categorical data were assessed for significance using the Chi-square test. Continuous data were tested for normality using D'Agostino and Pearson omnibus normality test. Due to the non-parametric nature of the data analysed in this study, the Mann-Whitney test was used to determine the statistical significance of differences in continuous data between groups. A *p* value of <.05 was considered significant in all analysis.

Logistic regression analysis was used to determine the significance of metformin use in our population that included use of other hypoglycaemic medication and age. The Omnibus Test of Model Coefficients and the Hosmer-Lemeshow goodness of fit test and Cox and Snell R-square tests were applied to assess the usefulness, with a result of <0.05 considered significant.

Power calculation

A *post hoc* power calculation using a sample size of 174 controls and 175 cases (Table 1) was conducted with a two-sided 95% confidence interval. Exposures of 60% and 44% (Table 1) in controls and cases, respectively, achieved an 85.2% normal approximation and normal approximation with continuity correction of 82.5%.

Ethical considerations

This project was submitted to Monash Health Human Research Committee Coordinator, with the application number 15182Q. It was deemed a quality and service

improvement activity, and thus did not require consideration by the Human Research Committee.

Results

Diverticular disease in patients with diabetes mellitus

Demographics

This study included 349 patients with both diabetes mellitus and diverticular disease. Of these, 174 had uncomplicated diverticulosis at time of CT scan, and 175 had acute diverticulitis. The diverticulosis group was significantly older than the diverticulitis group (72 (67–87) and 70 (51–79) years, respectively, *p* = .03). There was no statistically significant difference in gender between the disease groups (*p* = .23) (Table 1).

Use of diabetic medications

Diabetic treatment was significantly more common among patients with diverticulosis than patients with diverticulitis (86% compared to 73%, *p* = .02). Metformin use was also more common among patients with diverticulosis, than patients with diverticulitis. 60% of diverticulosis patients took metformin, whereas only 44% of diverticulitis patients were on metformin (*p* = .002) (Table 1).

There were no statistically significant differences in use of other hypoglycaemic drugs between the diverticulosis and diverticulitis groups (Table 1).

Direct logistic regression analysis was used to ascertain whether the difference in metformin use between the groups remained significant in the context of age and the use of other hypoglycaemic drugs. The model included four independent variables: age, metformin use, other oral hypoglycaemic use and insulin. The full model was statistically significant χ^2 (4, *n* = 349) = 17.51, *p* = .002, which indicates that it is an appropriate tool. As shown in Table 2, only metformin showed a unique contribution to the likelihood of diverticulitis. Metformin was associated with a statistically significant decrease in the incidence of diverticulitis with an odds ratio of 0.49 (*p* = .002) While age also had a statistically significant on likelihood of diverticulitis (*p* = .007), the magnitude of the impact was less than metformin use (OR: 0.97, CI: 0.96–0.99) (Table 2).

Dose of metformin

There was a non-significant trend towards lower incidence of diverticulitis in patients receiving higher rather than lower

Table 1. Diverticular disease in patients with diabetes mellitus.

	Uncomplicated diverticulosis (<i>n</i> = 174)	Acute diverticulitis (<i>n</i> = 175)	<i>p</i> value
Age (years), median (IQR)	72 (67–87)	70 (51–79)	.03
Male, <i>n</i> (%)	101 (59)	90 (52)	.23
Any diabetic treatment <i>n</i> (%)	123 (86)	79 (73)	.02
Metformin <i>n</i> (%)	104 (60)	77 (44)	.002
Metformin dose (<i>n</i> = 169) (g/day), median (IQR)	1.5 (1.0–2.0)	1.0 (0.5–1.0)	.20
Oral hypoglycaemics <i>n</i> (%)	62 (36)	51 (29)	.12
Insulin <i>n</i> (%)	39 (23)	46 (27)	.24
HbA1C % (<i>n</i> = 77), median (IQR)	7.1 (6.8–8.2)	7.1 (4.8–7.1)	.38
eGFR <30	8 (8)	11 (7)	.44
60 mL/min/1.73 m ² (<i>n</i> = 256), <i>n</i> (%)			

Table 2. Multivariable analysis, diverticular disease in patients with diabetes mellitus.

	B	S.E.	Wald	Df	Sig.	Exp (B)	95% C.I. for EXP(B)	
							Lower	Upper
Age	-0.03	0.01	7.23	1	0.007	0.97	0.96	0.99
Other oral hypoglycaemic	-0.15	0.24	0.39	1	0.54	0.86	0.54	1.38
Insulin	-0.08	0.26	0.10	1	0.75	1.09	0.66	1.80
Metformin	-0.71	0.23	9.78	1	0.002	0.49	0.32	0.77
Constant	2.25	0.72	9.78	1	0.002	9.50		

Table 3. Diverticulitis in patients with diabetes mellitus.

	Uncomplicated (n = 135)	Complicated (n = 33)	p value
Age, median (IQR)	71 (62–79)	66 (58–73)	.07
Male (%)	69 (51)	22 (67)	.17
Length of stay (days), median (IQR)	3 (4)	11 (15)	<.0001
Metformin (%)	59 (44)	16 (48)	.48
Metformin dose (n = 74) (g/day), median (IQR)	1.00 (1.0–2.0)	1.00 (0.9–2.0)	.53
Oral hypoglycaemics (%)	42 (31)	8 (24)	.60
Insulin (%)	36 (27)	8 (24)	.44
HbA1C % (n = 38), median (IQR)	7.1 (6.3–7.8)	7.3 (6.2–7.7)	.87
eGFR <30 mL/min/1.73 m ² (n = 155), n (%)	10 (8)	1 (3)	.64

doses of metformin (median 1.0 g/day (1.0–2.0) vs. 1.5 g/day (0.5–1.00), $p = .20$).

Severity of diabetes

There were 77 patients with Haemoglobin A1C (HbA1C) available for analysis and 256 patients with eGFR measurements. There was no significant difference in HbA1C levels or incidence of renal failure (eGFR <30) between the diverticulosis and diverticulitis groups ($p = .38$ and $p = .44$, respectively) (Table 1).

Complications in patients with diabetes mellitus and diverticulitis

Of the 168 patients with moderate or severe diverticulitis, 135 had uncomplicated disease and 33 had complicated disease. There were no significant differences in median age, gender or hypoglycaemic drug use between the uncomplicated and complicated diverticulitis groups. There was also no difference in metformin use between the groups.

There was no significant difference in median HbA1C level or incidence of renal failure between the uncomplicated and complicated diverticulitis groups ($p = .87$ and $p = .64$, respectively). Patients with diverticulitis complicated by abscess or perforation had a significantly longer median length of hospital stay than patients who did not; 11 days compared to 3 days, respectively ($p < .0001$) (Table 3).

Discussion

This was a retrospective, hypothesis generating case-control study designed to assess the utility of metformin in the prevention of diverticulitis. We demonstrated an association between metformin use and lower incidence of diverticulitis, in diabetic patients with diverticular disease. This finding remained significant when the potential confounders: age, gender and use of other hypoglycaemic medication were

taken into account, suggesting a protective effect of metformin against diverticulitis in this patient group.

This must be considered within the context of any diabetic treatment being more common within the diverticulosis group, which raises the possibility of diabetes severity, rather than metformin use, reducing the likelihood of diverticulitis. However, given the similar rates of other oral hypoglycaemic and insulin use between the diverticulosis and diverticulitis groups, this explanation seems unlikely. This is further supported by similarity of HbA1C levels between the diverticulosis groups and diverticulitis groups, suggesting that diabetic severity is not associated with the incidence of diverticulitis. It is important to acknowledge that only a small proportion of patients had HbA1C levels available for analysis, so it is difficult to draw absolute conclusions from this data.

Another possible explanation for the higher incidence of metformin use in the diverticulosis group is that more diverticulitis patients have comorbid, confounding renal failure, which contraindicates the use of metformin. The majority of patients had eGFR information available, and there was not a higher incidence of renal failure in the diverticulitis group suggesting this is not a contributory factor.

The trend towards an association between lower doses of metformin and diverticulitis compared with diverticulosis suggests a dose-response relationship may exist but requires larger numbers of patients to be studied. We also did not find a significant difference in metformin use between the uncomplicated and complicated diverticulitis groups. It is possible that this is due to an insufficient sample size. A larger study of diabetic patients with diverticulitis could better define this relationship.

While there was also a statistically significant difference in age between the diverticulosis and diverticulitis groups, the magnitude of the difference was so low it is not clinically significant.

Recent basic science research suggests the oral hypoglycaemic drug, metformin, may have anti-inflammatory and antitumor activity. Metformin has been shown to reduce

pathological inflammation in the cardiovascular system, [13] the kidneys, [14] the colon [9] and the epithelium of the middle ear [15]. The microflora modulating and anti-inflammatory effects of metformin have been well described in both diabetic but also non-diabetic patient groups [16]. This is the first study to examine the use of metformin in diverticular disease. Our findings in diverticular disease are consistent with the anti-inflammatory actions of metformin described in these other disease states.

Diverticulitis is a condition that results in significant morbidity and mortality. While some risk factors have been established, the pathogenesis of diverticulitis has not been fully elucidated. There are currently no accepted strategies for the prevention of initial or recurrent episodes of diverticulitis in patients with diverticulosis.

In conclusion, this study showed metformin use was more common in patients with uncomplicated diverticulosis compared to acute diverticulitis patients. While this is an interesting finding, due to its retrospective design, this study does not provide evidence for causation. Metformin is an inexpensive, readily available drug, with a well-established safety profile, and so warrants further investigation. Because metformin is not widely used outside of the diabetic population, further research to apply this finding to a wider patient group is likely to require a prospective, interventional design. The best way to investigate the efficacy of metformin in the prevention of acute diverticulitis would be a randomised, placebo-controlled trial in patients who have had an episode of acute diverticulitis.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Additional discussion in light of new work

Recently Barbara *et al.*,¹³⁷ published work which investigated the colonic microbiota profile of patients with diverticular disease. The authors showed a reduced abundance of *Akkermansia* in the peridiverticular area in patients with SUDD, compared to distant colon sites, which was not present in patients with asymptomatic diverticulosis. We also note the negative correlation between *Akkermansia* abundance and macrophage count in the diverticular area, congruous with the previously described anti-inflammatory effects of *Akkermansia* in the colon.²⁵⁷

These findings are of particular interest to our group in the context of our study, which demonstrated a decreased incidence of metformin use in diabetics with diverticulitis compared to uncomplicated diverticulosis. While our study was not able to establish causation due to its retrospective nature, we believe that Barbara *et al.*'s work provides a plausible mechanism by which metformin could reduce peri-diverticular inflammation in patients with diverticular disease.

Metformin has been shown to increase *Akkermansia* levels in the colon in both humans and animal models.²⁵⁸ It is possible that, in this way, by addressing the deficit in colonic *Akkermansia* population in SUDD, as described by Barbara *et al.*, metformin could provide beneficial anti-inflammatory effects to this group. We believe that further prospective investigation of the effect of metformin on the colonic microbiota in patients with diverticular disease, and of its clinical utility in the management of SUDD, and the prevention of acute diverticulitis, is warranted.

Conclusion

Our study, particularly in the context of the recent work discussed, provides evidence that metformin may be a useful therapy to reduce the incidence of acute diverticulitis. It is possible that this can be explained by metformin's gut microflora modulation properties, which have the potential to reduce colonic inflammation. It is consistent with previous work that has described metformin's anti-inflammatory properties. As discussed, a prospective randomised control trial would be required to assess the clinical utility of metformin in the patients.

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Chapter 4: Body composition at the diagnosis of pancreatic malignancy

Introduction

The previous chapter (chapter 3) described the body composition phenotypes associated with diverticular disease: diverticulosis and the acute inflammatory manifestation diverticulitis. Here, body composition phenotypes associated with another inflammatory intra-abdominal pathology: pancreatic ductal adenocarcinoma are explored. The role of body composition in non-functioning pancreatic neuroendocrine tumours, a disease that has not been so well defined is also investigated. In particular, we assessed the relationship between body composition in localised and in malignant disease.

While the ability to measure and define individual adipose and skeletal muscle tissue area is useful in characterising individual or groups of patients, in isolation, these measurements are an insufficient measurement of patient wellbeing. This chapter presents a more complete picture of the nutritional and functional status of patients at the time of diagnosis of their PDAC. Peak expiratory flow (PEF), a simple, inexpensive bedside test, as an important measure of function was measured, to seek to validate against a gold standard measure of muscle function, handgrip strength.

4.1 Pancreatic neuroendocrine tumours are associated with different body composition phenotypes to pancreatic ductal adenocarcinomas

Introduction

Pancreatic neuroendocrine tumours (PNET) arise from pancreatic islet cells, and account for between two and five percent of all pancreatic malignancies. This equates to a clinical population incidence of approximately two per million,¹ in contrast to an incidence of 1.5% on autopsy.² This high proportion of undiagnosed PNETs speaks to the indolent course of the majority of these tumours. However, metastatic disease at diagnosis follows an aggressive path and carries a poor prognosis, with a 5-year survival rate of 40% compared to 93% when disease is localised at diagnosis.³

Pancreatic ductal adenocarcinoma (PDAC) on the other hand, carries a poor prognosis both when diagnosed as advanced metastatic disease, and when diagnosed when diagnosed as localised disease. The patients with stage 1, resectable disease have a 5-year survival rate of 27%, compared to those with advanced disease who have a 2% 5 year survival rate.⁴

While the cancer cachexia syndrome has been described in some form in both PDAC and advanced PNET,^{5,6} the rarity of the diagnosis of PNET compared to other malignancies, combined with its usually benign course, has resulted in a relatively limited body of surrounding literature.

There are a number of reasons why muscle wasting and weight loss are so characteristic of PDAC. The first is that malnutrition is common in this patient group. Malnutrition is complex, and multifactorial syndrome. Anxiety surrounding poor prognosis, abdominal pain, fatigue, duodenal stenosis, pancreatic exocrine insufficiency, malabsorption and constipation, have been

identified as significant, independent contributors to malnutrition in pancreatic cancer patients.⁷⁻⁹ Secondly, PDAC is a highly inflammatory tumour (ref), which is a key driver of muscle wasting.¹⁰ And thirdly, due to its aggressive nature, the rapid growth and energy requirement of PDAC and its surrounding desmoplasia, drives a hypercatabolic state in the body.¹¹ The extent to which these factors apply to PNET is unclear.

A number of retrospective studies have identified low muscle mass at diagnosis, as well as a reduction in muscle mass during the course of disease, to be poor prognostic factors in PDAC.¹²⁻¹⁵ Myosteatorsis, however, has not been so well investigated in pancreatic cancer. An association between myosteatorsis and poorer prognosis in pancreatic cancer was recently demonstrated by Lobo et al.¹⁶ The retrospective design of their study, however, has been criticised for its inability to include muscle function in analysis¹⁷ and so requires prospective replication. To our knowledge, there is no current published literature describing body composition phenotypes in PNET.

Methods

Patient identification and characterisation

Patients with non-functioning pancreatic neuroendocrine tumours (PNET) were identified prospectively and stored on a unit database. All patients with a diagnosis of PNET between 2004 and 2017 were considered. Patients with a past history of other neuroendocrine tumours, or with a diagnosis of a neuroendocrine tumour related syndrome were not included.

Patients with a diagnosis of pancreatic ductal adenocarcinoma (PDAC) were identified retrospectively, using an ICD-10 coding search (C25, malignant neoplasm of pancreas). The presence of a tissue diagnosis was confirmed by a review of medical records. These patients were case matched to the patients with PNET, based on age, gender and localised or metastatic disease status.

Patients for the control group were identified using a search of the hospital database for 'MVA' and 'motor vehicle accident'. Patients were case matched to PNET patients 2:1(control:PNET) based on gender and age.

Scanned medical records were reviewed to record patient demographic and co-morbid disease information. Only patients with an abdominal computed tomography (CT) at the time of diagnosis or admission for motor vehicle accident were included.

Body composition analysis

Body composition analysis was performed using L3 CT DICOM and SliceOmatic software (TomoVision, USA). Subcutaneous fat was identified using the Hounsfield unit (HU) thresholds -190 to -30, and to identify subcutaneous and extramyocellular fat (EMCF) -150 to -50 HU were used. Muscle was identified by isolating tissue between -29 and +150 HU. Skeletal muscle index (SMI) was

calculated using the formula $SMI = L3 \text{ skeletal muscle area (cm}^2\text{)} / \text{height (m)}^2$, and the SMI cut offs of <38.5 in women and <52.4 in men were used to determine sarcopenia, as previously defined by Prado *et al.*¹⁸

Statistical analysis

All statistical analysis was performed using SPSS v24 (IBM) statistical software. Continuous data was tested for normality and given its non-parametric nature, is presented as median (interquartile range). Given the non-parametric nature of this data, the Kreuskal-Walis rank test was used to determine significance of relationship between 3 groups. If there was not a significant difference between groups, the p value from this test is presented. When significance was determined the Mann-Whitney U test was used to determine significance of each relationship. All categorical data is presented as number (percentage). The chi-square test was used to determine significance of relationship between categorical variables. A p value of less than 0.05 was considered significant for all analysis. A multivariable analysis of variance (MANOVA) was used to determine which factors had a significant impact on muscle function (handgrip strength) in this group.

Ethical considerations

The following study is a culmination of data from two human research ethics committee approved projects, with the reference numbers RES-17-0000-539Q and 16033L.

Results

Controls, localised and metastatic PNET

There were 52 patients with non-functioning PNET included, of which 38 had localised disease and 14 had metastatic disease. These patients were matched 2:1 to 104 control patients. There was no significant difference in gender or

age between the localised and metastatic PNET groups. The size of primary PNET in the metastatic group (median 37mm) was not significantly different than the localised group (median 22mm, $p=0.2$). *Table 1.*

There was no difference in visceral fat area (VFA) between the control and localised PNET groups (197.2cm^2 v 183.9cm^2 respectively). The median VFA of the metastatic PNET group (70.7cm^2) was, however, significantly less than both the control and localised groups. Similarly there was no difference in subcutaneous fat area (SCFA) between the control and localised PNET groups (197.2cm^2 v 242.5cm^2), but the metastatic group had significantly lower SCFA than both groups (77.9cm^2). There was no difference in extramyocellular fat area (EMCF), skeletal muscle area or skeletal muscle index (SMI) between the groups. However, sarcopenia was significantly more common in patients with metastatic PNET (67%), compared to those who had localised disease (18%). *Table 1.*

	Control (n=104)	Localised PNET (n=38)	Metastatic PNET (n=14)	p value
Age (years), median (IQR)	63 (57-73)	63 (56-72)	65.0 (55-71)	1.0
Male, n (%)	60 (58)	19 (50)	11 (79)	0.2
Size of primary PNET (mm), median (IQR)	N/A	22 (15-41)	37 (20-54)	0.2
VFA (cm ²), median (IQR)	197.2(115.3- 246.8)+^	183.8 (115.0- 246.8)+*	70.7 (45.2- 193.7)*^	+0.2 *0.03 ^0.02
SCFA (cm ²), median (IQR)	197.2(115.3- 246.8)+^	242.5 (153.0- 316.4)+*	77.9 (53.1- 241.4)*^	+0.7 * 0.04 ^0.03
EMCF (cm ²) median (IQR)	8.8 (5.4-16.2)	9.1 (6.0-13.4)	8.2 (2.7-15.0)	0.7
SkMA (cm ²) median (IQR)	131.1 (110.6- 173.3)	135.9 (114.3- 167.6)	139.9 (112.6- 184.0)	0.8
SMI (cm ² /m ²) median (IQR) n=143	47.2 (41.2- 54.0)	48.4 (43.0- 55.1)	48.5 (38.5- 57.2)	0.9
Sarcopenic, n (%) n =143	33 (34)+^	6 (18)+*	8 (67)*^	+0.7 *0.002 ^0.05
Myosteosis median (IQR)	0.06 (0.04- 0.14)	0.06 (0.04- 0.11)	0.05 (0.02- 0.11)	0.6

Table One: Pancreatic neuroendocrine tumour metastases

Abbreviations: Pancreatic neuroendocrine tumour (PNET), interquartile range (IQR), visceral fat area (VFA), subcutaneous fat area (SCFA), extramyocellular fat area (EMCF), skeletal muscle area (SkMA), skeletal muscle index (SMI)
Myosteosis = EMCF/SkMA

Control, localised and metastatic PDAC

Fifty-two patients with PDACs were case matched to the 52 patients with PNETs, based on age, gender and localised/metastatic disease status. When compared to the case matched motor vehicle accident controls and between localised and metastatic PDAC, patients with metastatic PDAC had significantly higher levels of visceral fat (246.9cm²), than the patients with localised PDAC (145.2 cm²). There were no differences in median subcutaneous or extramyocellular fat levels between the groups. There was also no difference in skeletal muscle area or SMI between the PDAC or control groups. Sarcopenia was significantly more common (64% of patients) in the metastatic PDAC group than the control group (34% of patients). While sarcopenia was also more common in the localised PDAC group (47% of patients) than the control group, this difference was not statistically significant. *Table 2.*

	Control (n=104)	Localised PDAC (n=38)	Metastatic PDAC (n=14)	p value
Age (years), median (IQR)	63 (57-73)	63 (56-72)	65 (56-70)	1.0
Male, n (%)	60 (58)	19(50)	11 (79)	0.2
VFA (cm ²), median (IQR)	197.2(115.3- 246.8)+^	145.2(69.3 - 229.3)+*	246.9 (161.6- 339.4)^*	+0.03 ^0.09 * 0.006
SCFA (cm ²), median (IQR)	197.2(115.3- 246.8)	200.4 (118.9- 252.4)	246.9 (161.6- 339.4)	0.2
EMCF (cm ²) median (IQR)	8.8 (5.4-16.2)	8.2 (5.1-13.5)	8.5 (3.8-15.8)	0.6
SkMA (cm ²) median (IQR)	213.2(145.0- 302.1)	119.1 (103.2- 149.1)	177.9 (117.9- 311.6)	0.09
SMI (cm ² /m ²) median (IQR) n=147	47.2 (41.2- 54.0)	45.2 (38.4- 53.0)	39.1 (130.3- 169.6)	0.4
Sarcopenic, n (%) n=147	33 (34)+^	17 (47)+*	9 (64)^*	+0.1 ^0.03 *0.3
Myosteatosi median (IQR)	0.06 (0.04- 0.14)	0.08 (0.04- 0.11)	0.06 (0.03- 0.11)	0.5

Table Two: Pancreatic ductal adenocarcinoma localised and metastatic disease compared to controls

Abbreviations: pancreatic ductal adenocarcinoma (PDAC), interquartile range (IQR), visceral fat area (VFA), subcutaneous fat area (SCFA), extramyocellular fat area (EMCF), skeletal muscle area (SkMA), skeletal muscle index (SMI)
Myosteatosi = EMCF/SkMA

Localised pancreatic malignancies

There were no differences in absolute fat or muscle areas between localised PNET and PDAC, and their case matched controls. However, sarcopenia was significantly more common in localised PDAC (47%), than localised PNET (18%). *Table 3.*

	Control (n=76)	Localised PNET (n=38)	Localised PDAC (n=38)	p value
Age (years), median (IQR)	64 (56-73)	63 (56-72)	63 (56-72)	N/A
Male, n (%)	38 (40)	19 (40)	19(40)	N/A
VFA (cm ²), median (IQR)	191.9 (111.7- 239.6)	183.8 (115.0- 246.8)	145.2(69.3 - 229.3)	0.2
SCFA (cm ²), median (IQR)	236.0 (154.9- 314.9)	242.5 (153.0- 316.4)	200.4 (118.9- 252.4)	0.2
EMCF (cm ²) median (IQR)	9.6 (6.7- 16.4)	9.1 (6.0-13.4)	8.2 (5.1-13.5)	0.4
SkMA (cm ²) median (IQR)	127.5 (108.5- 168.5)	135.9 (114.3- 167.6)	119.1 (103.2- 149.1)	0.2
SMI (cm ² /m ²) median (IQR) n=142	46.8 (40.3- 53.0)	48.4 (43.0- 55.1)	45.2 (38.4- 53.0)	0.3
Sarcopenic, n (%) n=142	23 (32)+^	6 (18)+*	17 (47)^*	+0.1 ^0.07 *0.006
Myosteatosis median (IQR)	0.07 (0.04- 0.14)	0.06 (0.04- 0.11)	0.08 (0.04- 0.11)	0.6

Table Three: Localised PDAC and PNET v controls

Abbreviations: Pancreatic neuroendocrine tumour (PNET), interquartile range (IQR), visceral fat area (VFA), subcutaneous fat area (SCFA), extramyocellular fat area (EMCF), skeletal muscle area (SkMA), skeletal muscle index (SMI)
Myosteatosis = EMCF/SkMA

Metastatic pancreatic malignancies

Metastatic PNETs were associated with a significantly lower VFA, than both the control group and the metastatic PDAC group (70.7cm² compared to 203.7 cm² and 246.9 cm² respectively). There were no other significant differences between fat or muscle tissues between the groups. While sarcopenia was more prevalent in the metastatic PNET (61%) and metastatic PDAC (64%) groups than the control group (38%), these differences were not statistically significant.

	Control (n=28)	Metastatic PNET (n=14)	Metastatic PDAC (n=14)	p value
Age (years), median (IQR)	66 (58-69)	65(55-71)	65 (56-70)	N/A
Male, n (%)	22 (79)	11 (79)	11 (79)	N/A
VFA (cm ²), median (IQR)	203.7 (126.0- 296.6)+^	70.7 (45.2- 193.7)+*	246.9 (161.6- 339.4)*^	+0.04 ^0.2 *0.01
SCFA (cm ²), median (IQR)	191.5 (125.0- 275.8)	77.9 (53.1- 241.4)	177.9 (117.9- 311.6)	0.3
EMCF (cm ²) median (IQR)	7.4 (4.0- 13.7)	8.2 (2.7-15.0)	8.5 (3.8-15.8)	0.9
SkMA (cm ²) median (IQR)	150.7 (118.0- 184.1)	139.9 (112.6- 184.0)	139.1 (130.3- 169.6)	0.9
SMI (cm ² /m ²) median (IQR) n=54	52.3 (45.0- 56.8)	48.5 (38.5- 57.2)	47.2 (43.9- 52.2)	0.5
Sarcopenic, n (%) n=54	10 (38)^	8 (61)	9 (64)	0.2
Myosteatosi median (IQR)	0.04 (0.02- 0.1)	0.05 (0.02- 0.11)	0.06 (0.03- 0.11)	0.9
<p>Table Four: Metastatic PDAC and PNET v controls Abbreviations: Pancreatic neuroendocrine tumour (PNET), interquartile range (IQR), visceral fat area (VFA), subcutaneous fat area (SCFA), extramyocellular fat area (EMCF), skeletal muscle area (SkMA), skeletal muscle index (SMI) Myosteatosi = EMCF/SkMA</p>				

Discussion

To our knowledge this is the first study to examine body composition phenotypes in non-functioning PNET. This study compares body composition in PNET to both an age and gender matched control group, as well as an age, gender, and disease status matched PDAC group. We believe that this allows for interesting comparison between to biologically very different tumours, arising the same organ, and their effect on the body. At the same time, however, it is important to recognise that because the PDAC groups were case matched to the PNET groups they are not representative of the whole PDAC population. Firstly this study demonstrated that metastatic PNET is associated with significantly lower levels of both visceral and subcutaneous fat, as well as a higher incidence of sarcopenia than localised disease. This difference in body composition phenotype is consistent with the vastly different disease behaviour and resultant prognosis in localised and metastatic disease. It is important to note that while there was no difference in median SMI between the groups, when gender specific sarcopenic cut offs were applied, the clear difference in sarcopenia prevalence became apparent. This was due to the higher proportion of males in the metastatic group, concealing the relatively low muscle mass in these patients. This illustrates the importance of gender specific skeletal muscle analysis.

The dramatically lower levels of both visceral and subcutaneous fat between the in the metastatic PNET group compared to the localised PNET group is also interesting, as is the lower visceral fat level in the metastatic PNET group compared to the metastatic PDAC group. Cancer cachexia syndrome, which has been well described in many advanced malignancies, but not in PNET, describes the disproportionately high loss of lean tissue compared to adipose tissue, driven by inflammatory mediated catabolism.¹⁶ The loss of

predominantly adipose tissue, with a relative maintenance of muscle tissue is a feature of starvation (when energy requirements exceed calorie intake), rather than inflammatory, catabolic disease states.¹⁷ It is possible that the body composition phenotype we have described in metastatic PNET can be explained by the high-energy requirement of the neoplastic cells, in the absence of systemic inflammation that is so typical of PDAC and other malignancies associated with cachexia. Another possibility is that these 'non-functional' PNETs are in fact secreting factors, which in localised disease are hepatically metabolised and rendered inactive. These factors could potentially be hormones, inflammatory cytokines or adipocytokines. When the PNET metastasizes to the liver, these factors may be present in the systemic blood stream, thereby altering metabolic processes, and potentially producing the described body composition changes. This is similar conceptually to carcinoid syndrome, which mainly occurs in patients with hepatic metastases capable of secreting serotonin directly into the post-portal systemic circulation, allowing the serotonin to circulate throughout the body and act on receptors in end organs, before being hepatically metabolised.¹⁹

Retrospective body composition studies rarely include a healthy control group, due to the difficulty in identifying healthy populations with an abdominal CT scan available. To our knowledge, this is the first time that motor vehicle accident victims have been used for this purpose. There are some potential confounders in this group that may skew body composition data. For example peripheral neuropathy associated with poorly controlled diabetes mellitus may lead to increase risk of motor vehicle accident and also be associated with a different body composition phenotype. However, we believe that these confounders are likely to be of minimal significance, and that this control group functions as a reasonably good representation of the general Australian population.

As discussed, due to its relative rarity, PNET is a difficult disease to study. This study presents interesting differences in body composition phenotype associated with both histological diagnosis and disease stage between PNET and PDAC. This difference in the body's response to disease, speaks to the vastly different nature of these two malignancies of the pancreas. Further work to validate and understand the dramatic fat loss that we have described in metastatic PNET, may shed light on the drivers of cancer cachexia, as well as the biological drivers of metastases in this disease.

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4.2 Functional assessment of pancreatic ductal adenocarcinoma patients

Background

Pancreatic ductal adenocarcinoma (PDAC) is a common cancer. The Australian population incidence is 11 per 100,000, making it the 11th most commonly diagnosed cancer in Australia.¹ In contrast to the general trend towards reduced incidence of cancers worldwide, the incidence of PDAC is increasing.^{2,3} Due to its poor survival rate, PDAC ranks much higher, 5th in Australia, in terms of cancer deaths.³ Worldwide, the mortality rate of pancreatic cancer is 96%.³ One of the most distressing features of pancreatic cancer, especially for patients and family is the cachexia and resultant sarcopenia, associated with the disease.

Cachexia and sarcopenia are the result of an imbalance between muscle protein synthesis and muscle protein breakdown. Cachexia describes the wasting process; it is a dynamic term, whereas sarcopenia describes muscle health at a given time, encompassing both size and function of skeletal muscle.⁴ The mechanism behind the pathological muscle loss that defines both conditions has not been fully defined. It is clear, however, that cachexia and sarcopenia are multifactorial processes involving a complex interplay between not only caloric input and output, but also genetic, endocrine, metabolic and inflammatory pathways.^{5,6} Alterations to taste and smell, in combination with symptoms of early satiety and nausea, all of which have been described in pancreatic cancer, contribute to a negative caloric imbalance. Due to the pancreas' important role in endocrine and exocrine modulation of metabolism, it is also feasible that the cachexia that is such a prominent feature of pancreatic cancer, is at least in part a result of the disruption in this complex system.⁷ Inflammation is central to the

pathophysiology of pancreatic cancer, functioning both as a risk factor for tumour genesis and progression, as well as consequence of the cancer.⁸

Muscle function is not commonly assessed as part of standard clinical management, and so research in this area must be performed prospectively. For this reason, research that involves a complete definition of sarcopenia is scarce. There is no clear consensus on how muscle function should be measured. Handgrip testing using a dynamometer is a well-validated tool to assess muscle strength. There is a significant body of literature that demonstrates an association between reduced grip strength and poor clinical outcomes⁹, these include: increased length of stay,¹⁰ functional decline,¹¹ morbidity¹² and mortality.¹² The use of peak expiratory flow measurement as a test for muscle strength is not so well validated. An association has been demonstrated between muscle strength and peak expiratory flow rate by one study,¹³ however there has been no validation of this finding. The European Working Group on Sarcopenia in Older People (EWGSOP) suggest that further study of peak expiratory flow rate as a marker of muscle function is required before it can become a standard measurement to be used as a prognostic tool.¹⁴

The aim of this study is to first investigate the relationship between stage of pancreatic malignancy (PDAC and PNET) and radiologic body composition parameters, at the time of diagnosis of disease. It then aims to more comprehensively define the nutritional, functional status of PDAC patients at diagnosis. This involves evaluating the established muscle function assessment, handgrip strength, alongside a more novel test of functional status in malignancy, peak expiratory flow.

Methods

Patient identification and characterisation

Patients with a tissue diagnosis of pancreatic ductal adenocarcinoma (PDAC) were recruited prospectively to this study within 30 days of diagnosis, and prior to surgery or chemotherapy commencement. Patients were recruited between March 2016 and September 2017. Written and verbal informed consent to participate in the study was obtained.

Scanned medical records were reviewed to record patient demographic and co-morbid disease information. Significant smoking was defined as either a current smoker, or a history of > 20 pack years.

Body composition analysis

Body composition analysis was performed using L3 CT DICOM and SliceOmatic software (TomoVision, USA). Subcutaneous adipose tissue was identified using the Hounsfield unit (HU) thresholds -190 to -30, and to identify subcutaneous and extramyocellular fat (EMCF) -150 to -50 HU were used. Muscle was identified by isolating tissue between -29 and +150 HU. Skeletal muscle index (SMI) was calculated using the formula $SMI = L3 \text{ skeletal muscle area (cm}^2\text{)} / \text{height (m)}^2$, and the SMI cut offs of <38.5 in women and <52.4 in men were used to define myopenia, as defined by Prado *et al.*²⁶²

Functional assessment of pancreatic ductal adenocarcinoma patients

Patients used their dominant hand to complete handgrip strength testing. Three measures of handgrip strength were recorded using a dynamometer. Only the highest of the three is reported. Low handgrip strength was defined as <20 kgs in women and <30 kgs in men, as per the European Working Group on Sarcopenia.⁵⁶ One measure of peak expiratory flow was recorded

using a peak expiratory flow meter. Patients were asked to report on a scale of 0 to 4 the extent to which statements regarding anorexia and weight loss risk applied to them in the last 7 days (FAACT questionnaire). We have defined a score of 0-1 as the statement not significantly applying to the patient, and a score of 2-4 as the statement significantly applying to the patient.

Sarcopenia was defined as the presence of both myopenia and low handgrip strength.

Statistical analysis

All statistical analysis was performed using SPSS v24 (IBM) statistical software. Continuous data was tested for normality and given its non-parametric nature, is presented as median (interquartile range). All categorical data is presented as number (percentage). A Mann-Whitney U test was used to determine significance of relationship between categories of continuous variables and a chi-square test was used to determine significance of relationship between categorical variables. Pearson's rank correlation was used to determine significance of association between continuous variables. A p value of less than 0.05 was considered significant for all analysis, except where noted in the text. A MANOVA was used to determine the significance of multiple variables pertaining to demographic and body composition in relation to muscle function.

Functional status at diagnosis of pancreatic ductal adenocarcinoma

Demographics

This study involved 85 patients at diagnosis of PDAC. The median age of the group was 73 years, and 46% of the patients were male. Of the group 38% were smokers, 33% were diabetic and 15% were on metformin. The median

BMI was 25.7 kg/m². 45% of the patients were myopenic and 22% of the patients were sarcopenic.

Table 10: Demographics

Demographic	Participants (N=85)
Age (years), median (IQR)	73 (63-77)
Male sex, n (%)	39 (46)
Smoker, n (%)	32 (38)
Diabetic, n (%)	28 (33)
Metformin, n (%)	13 (15)
BMI (kg/m ²), median (IQR)	25.7 (22.3-28.0)
Myopenic, n (%)	38 (45)
Sarcopenic, n (%)	19 (22)

Abbreviations: interquartile range (IQR), body mass index (BMI)

Anorexia and related symptoms

Of the 85 PDAC patients, 48% of patients reported that the statement “I have a good appetite” applied to them. 59% percent of patients felt that “the amount I eat is sufficient to meet my needs” applied to them, and 41% of patients felt that “I am worried about my weight”. The statement “most food tastes unpleasant to me” applied to 32% of patients and “I am concerned about how thin I look” to 36%. 53% of patients reported that “my interest in food drops as soon as I try to eat” was true and 55% agreed with the statement “I have difficulty eating rich or heavy foods”. 28% of patients agreed with “my family or friends are pressuring me to eat”, and 15% that “I have been vomiting”. The statement “when I eat, I get full quickly” was significant for 64% of patients, “I have pain in my stomach area for 55% of patients and “my general health is improving for 49% of patients. Of the 85

patients, only 5 patients reported experiencing none of the measured symptoms. The other 80 patients, representing 94% of the group reported experiencing at least one symptom. 87% of patients experienced at least two symptoms, 66% experienced at least four symptoms, 48% experienced at least six symptoms, 22% experienced at least eight symptoms and 12% at least ten symptoms. Only one of the 85 patients reported experiencing all twelve symptoms.

Table 11: Symptoms associated with anorexia

Statement, n (%)	Patients to whom statement applied (N=85)
I have a good appetite	41 (48)
The amount I eat is sufficient to meet my needs	50 (59)
I am worried about my weight	35 (41)
Most food tastes unpleasant to me	27 (32)
I am concerned about how thin I look	31 (36)
My interest in food drops as soon as I try to eat	45 (53)
I have difficulty eating rich or heavy foods	47 (55)
My family or friends are pressuring me to eat	24 (28)
I have been vomiting	13 (15)
When I eat, I get full quickly	54 (64)
I have pain in my stomach area	47 (55)
My general health is improving	43 (49)
Patients no measured symptoms	5 (6)
Patients with ≥ 1 symptoms	80 (94)
Patients with ≥ 2 symptoms	74 (87)
Patients with ≥ 4 symptoms	56 (66)
Patients with ≥ 6 symptoms	41 (48)
Patients with ≥ 8 symptoms	19 (22)
Patients with ≥ 10 symptoms	10 (12)
Patients with all measured symptoms	1 (1)

The relationship between anorexia symptoms and body composition

There was no difference in the prevalence of low BMI, myopenia or sarcopenia, between the patients who had three or less symptoms, compared to patients with 7 or more symptoms.

Table 12: Symptoms of anorexia and body composition

	≤ 3 symptoms (N=29)	≥ 7 symptoms (N=29)	p value
Low BMI, n (%)	4 (14)	4 (14)	0.1
Myopenic, n (%)	14 (48)	13 (44)	0.8
Sarcopenic, n (%)	7 (24)	6 (21)	0.9

Abbreviations: body mass index (BMI)
Low BMI < 20kg/m²

Is peak expiratory flow a useful measure of muscle function?

Peak expiratory flow had a strong, statistically significant, association with handgrip strength ($R = 0.7$, $P < 0.001$). Peak expiratory flow was also significantly higher in non-sarcopenic patients, than sarcopenic patients. (250 v 170 L/min, $p = 0.03$)

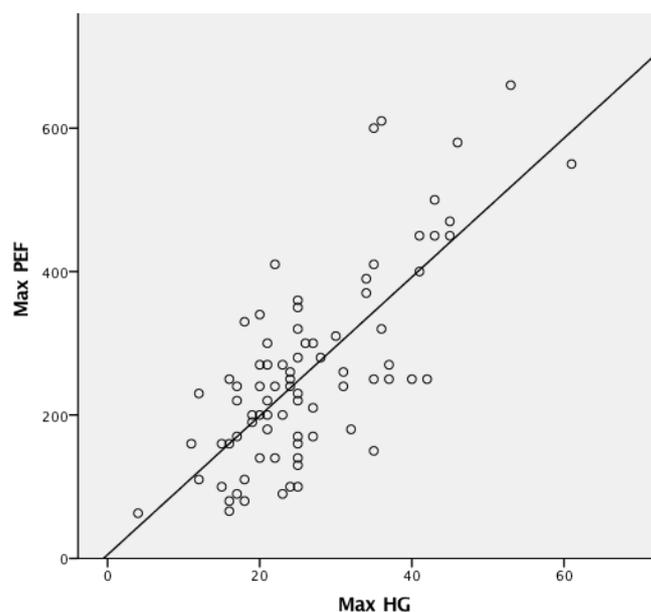


Figure 2: The relationship between handgrip strength and peak expiratory flow (PEF)
Results: $R^2 = 0.543$, $R = 0.737$, $p < 0.001$

Table 13: Peak expiratory flow in sarcopenia

	Non-sarcopenic N = 66	Sarcopenic N= 19	p value
PEF (L/min), median (IQR)	250	170	0.03
Abbreviations: peak expiratory flow (PEF), interquartile range (IQR)			

Muscle function and radiological muscle parameters

Both handgrip strength and peak expiratory flow were associated with SMI ($R=0.29$, $p=0.008$ and $R=0.22$, $p=0.047$, respectively). While handgrip strength was associated with mean skeletal muscle attenuation ($R=0.378$, $p=0.002$), peak expiratory flow was not associated with mean skeletal muscle attenuation ($p=0.095$). EMFA : skeletal muscle area was negatively associated with both handgrip strength ($R= -0.28$, $p=0.021$) and peak expiratory flow ($R= -0.27$, $p=0.021$).

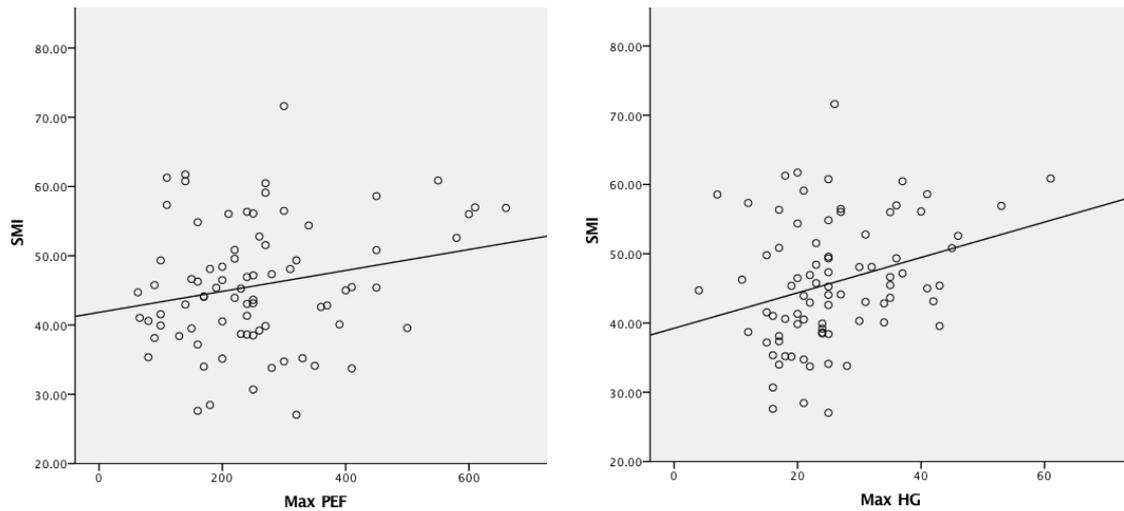


Figure 3A: Skeletal muscle index (SMI) and muscle function

A) The relationship between SMI and peak expiratory flow (PEF)

Results: $R^2 = 0.05$, $R = 0.22$, $p = 0.047$

B) The relationship between SMI and handgrip strength

Results: $R^2 = 0.083$, $R = 0.29$, $p = 0.008$

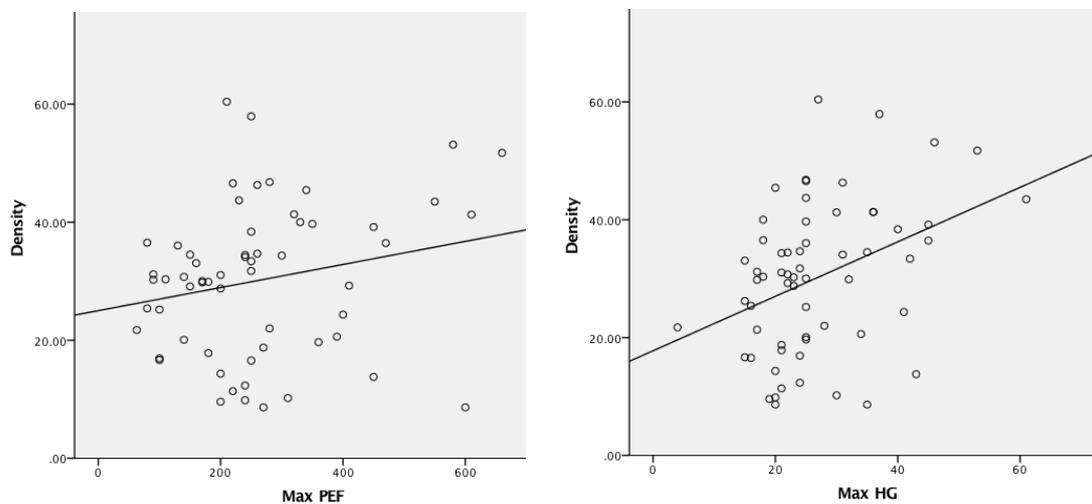


Figure 3B: Skeletal muscle attenuation and muscle function

A) The relationship between mean muscle attenuation and peak expiratory flow (PEF)

Results: $R^2 = 0.047$, $R = 0.218$, $p = 0.095$

B) The relationship between mean skeletal muscle attenuation and handgrip strength

Results: $R^2 = 0.143$, $R = 0.378$, $p = 0.002$

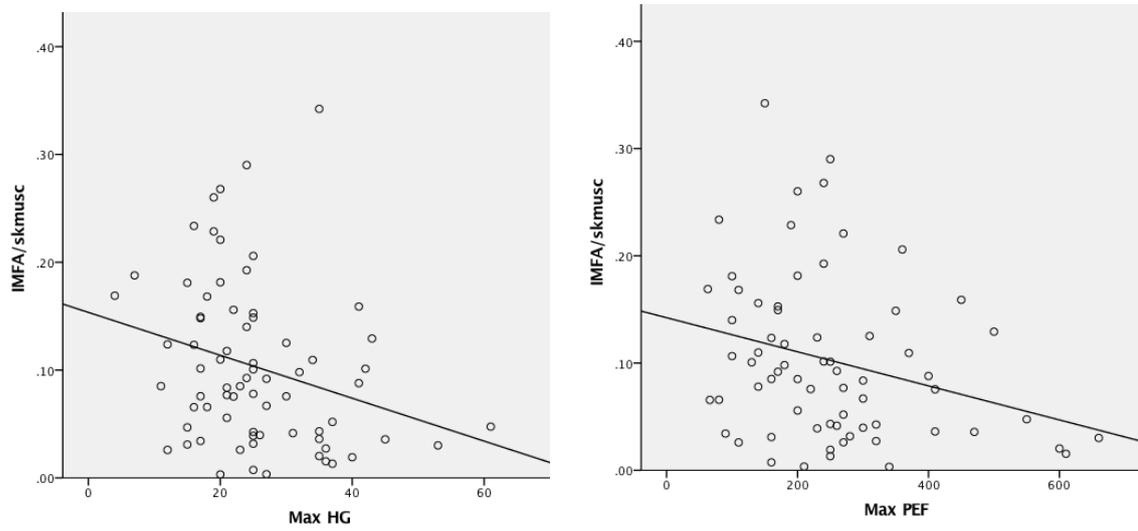


Figure 3C: Extramyocellular fat area (EMFA) to skeletal muscle area ratio and muscle function

A) The relationship between EMFA:skeletal muscle area and peak expiratory flow (PEF)

Results: $R^2 = 0.078$, $R = -0.28$, $p = 0.021$

B) The relationship between EMFA:skeletal muscle area and handgrip strength

Results: $R^2 = 0.074$, $R = -0.27$, $p = 0.021$

Smoking and body composition in pancreatic ductal adenocarcinoma

PDAC patients with a significant smoking history were significantly younger than those without a significant smoking history (74 years v 69 years, $p=0.008$). They also had a significantly lower BMIs (23.5 kg/m^2) than those without significant smoking histories (26.0 kg/m^2), ($p=0.08$), and significantly lower VFA ($p=0.04$), SCFA (0.08). There were not significant differences between radiological skeletal muscle parameters or muscle function.

Table 14: Body composition and smoking in PDAC

	No significant smoking history N= 53	Significant smoking history N= 32	p value
Age (years), median (IQR)	74 (65 – 80)	69 (58 – 74)	0.008
BMI (kg/m ²), median (IQR)	26.0 (23.1 – 28.2)	23.5 (21.2 – 26.7)	0.08
VFA (cm ²), median (IQR)	174.2 (98.1 – 244.6)	124.3 (75.7 – 174.3)	0.04
SCFA (cm ²), median (IQR)	204.0 (150.4 – 269.2)	172.5 (110.9 – 240.5)	0.08
EMFA (cm ²), median (IQR)	10.2 (4.8 – 16.8)	11.5 (7.2 – 15.6)	0.7
TFA (cm ²), median (IQR)	412.9 (264.4 – 502.1)	343.0 (207.1 – 481.9)	0.2
SMI (cm ² / m ²), median (IQR)	45.3 (38.7 – 55.7)	44.1 (40.0 – 49.5)	0.7
EMFA/SMA, median (IQR)	0.09 (0.03 – 0.15)	0.09 (0.04 – 0.14)	0.8
HGS (kg), median (IQR)	23 (17 – 35)	25 (21 – 31)	0.2
PEF (L/min), median (IQR)	235 (160 – 325)	240 (170 – 320)	0.8

Abbreviations: interquartile range (IQR), body mass index (BMI), visceral fat area (VFA), subcutaneous fat area (SCFA), extramyocellular fat area (EMFA), total fat area (TFA), skeletal muscle area (SMA), handgrip strength (HGS), peak expiratory flow (PEF)

MANOVA for handgrip strength

The multiple variable analysis was run to predict handgrip strength from age, gender, smoking history, SMI, mean muscle attenuation and EMFA : skeletal muscle area. In this model binary variables were assigned a value of 0 or 1: female gender and significant smoking were assigned the value 1.

Handgrip strength = $3.21 - (0.30 \times \text{age}) - (0.28 \times \text{gender}) + (0.77 \times \text{SMI}) - (0.76 \times \text{EMFA : skeletal muscle area}) + (1.17 \times \text{density})$

These model created statistically significantly predicted handgrip strength $F(5,85) = 5.02$, $p = 0.001$, $R^2 = 0.30$. Only two of the five variables, however, made a statistically significant contribution to the model: age ($t = -3.0$, $p = 0.004$) and gender ($p = 0.002$).

Discussion

Part One: Body composition at diagnosis of pancreatic malignancy

There was no difference in body composition between patients with non-metastatic PDAC and patients with metastatic PDAC. However, in PNET metastatic disease was associated with lower TFA, VFA and SCFA. There was no difference in muscle parameters between the patients with localised PNET and metastatic PNET.

The relative scarcity of adipose tissue, but not skeletal muscle, in metastatic PNET compared to localised PNET, is interesting. Cancer cachexia syndrome, which has been well described in many advanced malignancies, but not in PNET, describes the disproportionately high loss of lean tissue compared to

adipose tissue, driven by inflammatory mediated catabolism.¹⁶ The loss of predominantly adipose tissue, with a relative maintenance of muscle tissue is a feature of starvation (when energy requirements exceed calorie intake), rather than inflammatory, catabolic disease states.¹⁷ It is possible that the body composition phenotype we have described in metastatic PNET can be explained by the high-energy requirement of the neoplastic cells, in the absence of systemic inflammation that is so typical of PDAC and other malignancies associated with cachexia. Another possibility is that these 'non-functional' NETs are in fact secreting factors, which in localised disease are hepatically metabolised and rendered inactive. These factors could potentially be hormones, inflammatory cytokines or adipocytokines. When the PNET metastasizes to the liver they may disrupt these metabolic processes, resulting in higher concentrations of these 'active' factors in the blood stream, producing the described body composition phenotype.

In the PDAC groups there was no difference in body composition between patients with localised and metastatic disease, nor was any body composition parameter associated with tumour size. This is inconsistent with previous study by Bachmann et al, which showed an increased burden of metastatic disease in cachectic patients, discovered at time of planned curative operation.¹⁸ However this is different cohort to our study, which included all PDAC patients, not just operative candidates, making it difficult to draw conclusions from the differences in our findings. It is possible that our findings can be explained, at least in part, by the work by Berry *et al.*, who demonstrated marked homogeneity between the transcription profiles of endoscopic ultrasound guided aspirate from patients with localised and malignant PDAC.¹⁹ This is consistent with our work; both suggesting that there is little biological difference in localised and malignant tumours. The differences in extent of cancer cachexia between PDAC patients might instead

be explained by immunologic response to the malignancy²⁰ driving catabolism, rather than the tumour cells themselves. This immunologic response is likely to be moderated by host factors, rather than just tumour factors, and be the main driver of cachexia.

Due to their retrospective (PNET) and cross-sectional (PDAC) designs, these studies were unable to provide evidence regarding cause and effect; whether body composition parameters function as risk factors for pancreatic malignancy, or whether body composition phenotypes a result of the malignancy. Another limitation was, due to PNET's relative rarity, the PNET study had a small sample size. So while there were clear, statistically significant, differences in adipose tissue amount and distribution between patients with localised and metastatic disease, a larger study may have better identified subtle differences in skeletal muscle parameters. It is also important to note that while the handgrip strength cut offs were gender specific, they were not cancer specific.

Future research comparing the body composition of PDAC and PNET to healthy controls may help to better define the phenotypes associated with these pancreatic malignancies. Longitudinal studies, tracking body composition over time in both diseases may be beneficial in elucidating the impact of pancreatic malignancies on body composition.

Part Two: Functional status at diagnosis of pancreatic ductal adenocarcinoma

Firstly, this study demonstrated a high prevalence of symptoms associated with anorexia, at the time surrounding diagnosis of PDAC. In particular, the majority of patients agreed with statements describing early satiety. While there is a paucity of work in the area of the effectiveness of early nutritional

intervention in PDAC, Temel et al demonstrated a more than 2 month survival benefit (30%) in patients who received palliative care in combination with standard oncological management, compared with those that just received standard oncological management, from the time of diagnosis with non-small cell lung cancer.²¹ Further research into early, aggressive, symptom management to mitigate cancer cachexia, improve quality of life and prolong survival in PDAC is warranted. It is also important to acknowledge the heterogeneity in responses to anorexia related symptoms, which serves as a reminder of the importance of personalising nutritional counselling and intervention in this diverse patient group. However, at diagnosis patients who reported more symptoms of anorexia were not more likely to be underweight, myopenic or sarcopenic than those who did not. It is important to note that often the onset of symptoms triggers the diagnosis of PDAC. For this reason, it is possible that patients had not experienced the symptoms measured for long enough for them to influence body composition changes. On the other hand, as discussed in chapter 2, the weight loss associated with PDAC is multifactorial, and is not completely explained by a simple reduction in caloric intake. Other factors such as the catabolism caused by the PDAC, its surrounding desmoplasia, and the inflammatory response it triggers, may be more significant in relation to body composition changes. Further longitudinal study of this cohort may better define the relationship between body composition and symptoms associated with anorexia in PDAC.

The correlation between handgrip strength and PEF in cancer patients was first demonstrated by Norman et al.²² Our study replicated these results in a less heterogeneous group, just PDAC patients (compared to the wide range of malignancies in Norman's study), with handgrip strength correlating strongly with PEF, with, interestingly, no significant outliers. This close association

suggests that factors that result in a reduction PEF, such as smoking and respiratory disease,²³ result in a proportional reduction in handgrip strength.

Smoking in PDAC patients was associated with a significantly younger age at diagnosis, consistent with the well-described association between cigarette smoking and PDAC.² However, there was a trend toward improved peak expiratory flow in patients with a significant smoking history compared to those without. This is not consistent with the literature in healthy patients.²³ This might be explained by the younger age of the smokers, as increasing age is associated with a decrease in peak expiratory flow. Yadav *et al* estimate that 25% of all PDAC is attributable to cigarette smoking.²⁴ It is also possible that there is an intrinsic difference in the PDAC that is caused by cigarette smoking, that it is less damaging to muscle function than PDAC that has developed in the absence of cigarette smoking.

The results presented in this chapter are preliminary. The authors intend to extend this study prospectively, and assess the relationship between radiologic body composition phenotypes and muscle function at diagnosis of disease, and the outcomes chemotherapy toxicity and survival. While this study demonstrates that peak expiratory flow measures are consistent with handgrip strength, only in combination with prospective measures of outcome, will the authors be able to comment on the clinical utility of this measure for prognostication.

Conclusion

The first part of this work supports previous research that suggested little biologic difference between localised and metastatic PDAC, rather than in localised disease where there are micrometastases. Future research into patients with localised PDAC, who post-resection, do not go on to develop metastatic disease, may help to better elucidate the relationship between body composition and PDAC behaviour.

The second part of this study suggests that while PNET does appear to result in weight loss, it does not result in true cancer cachexia. Further longitudinal research is required to better describe the impact of PNET on body composition.

A significant proportion of patients are sarcopenic and exhibit associated symptoms, which put them at risk of weight loss, at the time of diagnosis of PDAC. This suggests that there is a need for nutritional intervention and aggressive symptom management from the time of diagnosis. Further research examining the impact of these interventions on outcome measures, such as extent of cancer associated cachexia, quality of life, chemotherapy toxicity and length of survival, would be beneficial. This study also demonstrated a strong association between handgrip strength and PEF. Analysis of the results of prospective study of the relationship between PEF and length of survival will clarify the clinical prognostic utility of PEF in PDAC.

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Chapter 5: Body composition and management of pancreatic ductal adenocarcinoma

5.1 The use of body composition analysis to reduce Gemcitabine Nab-Paclitaxel toxicity in pancreatic cancer

Introduction

The previous chapter described the body composition phenotypes associated with advanced PDAC. In this chapter we go on to explore ways that body composition analysis could be used to personalise and improve management in PDAC. Gemcitabine nab-paclitaxel (Gem-Nab-P) is one of the key regimens used to manage PDAC. Although it is given with palliative intent, Gem-Nab-P is associated with significant side effects including: fatigue, anorexia, nausea and vomiting, gastrointestinal upset, neuropathy and haematological disturbance (see chapter 2). The following study defines the relationship between Gem-Nab-P toxicity, body composition and chemotherapy dose. It was designed to investigate whether modifying the BSA derived dose of Gem-Nab-P, by including skeletal muscle mass in the equation, would be beneficial in reducing serious adverse events associated with treatment. There is strong evidence that sarcopenic patients experience higher rates of chemotherapy toxicity than non-sarcopenic patients. This study explores whether this can be explained by alterations in the volume of distribution of this predominantly hydrophilic regimen, which theoretically will remain largely within lean tissues. It is possible that by excluding adipose tissue from the dosing equation, Gem-Nab-P could be given with greater precision, reducing toxicity in some patients.

Gemcitabine-nab-paclitaxel toxicity is not associated with body composition in pancreatic cancer

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Background

The chemotherapy combination of gemcitabine and nab-paclitaxel (Gem-Nab-P) is a common regimen in the treatment of metastatic pancreatic ductal adenocarcinoma (PDAC). Whilst considered less toxic than the alternative combination metastatic PDAC regimen (FOLFIRINOX: fluorouracil, folinic acid, irinotecan and oxaliplatin),²⁰⁹ and used as a palliative treatment, Gem-Nab-P is still associated with significant toxicity.²⁰⁶

There is heterogeneity among PDAC patients' responses to Gem-Nab-P treatment, both in terms of anti-tumour effect and toxicity.²⁰⁷ While this is likely to be multifactorial, it is possible that differing responses can be partially explained by variations in serum drug levels, as a result of differing drug volume of distribution, dependant on body composition phenotype.

Body surface area (BSA), a figure derived from height and weight, was established using animal models, and has been used to dose chemotherapy since its inception.²⁷⁰ BSA has a limited ability to distinguish individual body composition phenotypes, which, with the rising prevalence of obesity,²⁷¹ are becoming increasingly varied. This is particularly important in PDAC due to

its association with both pre-morbid obesity,²⁷² and, as a result of the disease, myopenia (low muscle mass).²⁴¹

Prado *et al.* demonstrated that a high fluorouracil to lean body mass (LBM) ratio is associated with first cycle toxicity in a cohort of 62 patients.²⁵⁰ The relationship between chemotherapy dose to LBM ratio and body composition has not been described in PDAC, or in any gemcitabine-based chemotherapy regimens. We sought to elucidate the relationship between body composition, Gem-Nab-P dose and outcomes in this group.

Methods

This was a dual-site, retrospective cohort study of patients with a tissue diagnosis of pancreatic ductal adenocarcinoma, who had combination Gem-Nab-P as a first-line therapy. Only patients with a computed tomography (CT) scan that included spinal level L3 and was performed within 3 months of chemotherapy commencement were included. Demographic and cancer treatment information was collected using electronic medical records and standardised adverse event screening tools, in addition to pathology and radiology databases.

Toxicity was defined as a grade 3 or 4 adverse event according to the National Cancer Institute Common Toxicity Criteria Adverse Events manual (CTCAE v4.0). This study only examines the first cycle of chemotherapy, to exclude possible confounding caused by dose or regimen changes after the first cycle.

Body composition analysis was performed using single slice CT techniques. Axial slices at spinal level L3, in Digital Imaging Communication in Medicine format were imported into SliceOmatic 4.3 (Tomovision, Canada) software.

The attenuation thresholds -29 to +150 Hounsfield units (HU) were used to segment muscle. Adipose tissue was manually identified according to its anatomical location, in relation to the abdominal muscle wall. Cross sectional areas of each tissue type were recorded, as well as the mean skeletal muscle HU (muscle attenuation). A single, experienced operator conducted all analysis. This method of body composition analysis has been validated for the measurement of adipose tissue and muscle areas in cancer patients.²⁶² Skeletal muscle index (SMI) was calculated by dividing cross-sectional muscle area by the patient's height squared ($SMI = \text{muscle area (cm}^2\text{)}/\text{height(m)}^2$). The sex specific cut offs for myopenia, previously described as significant in survival for solid gastrointestinal tract tumours by Prado *et al.* of: $SMI < 38.5 \text{ cm}^2/\text{m}^2$ for women and $SMI < 52.4 \text{ cm}^2/\text{m}^2$ for men, were used.²⁷³

All statistical analysis was performed using SPSS statistics (IBM, USA), version 22. The significance of relationship between categorical variables were compared using chi-square test. Group medians were compared using the Kruskal-Wallis test. Strength of association between categorical variables was determined using Pearson's rank correlation test. A p value < 0.05 was considered significant in all analyses with data displayed as median values with interquartile ranges.

Results

Demographics

This study included 52 patients with pancreatic, who had first line combination gemcitabine and nab-paclitaxel therap. The median age was 64.5 years (56.8-73.0) and 47% of the patients were male. The median body mass index (BMI) was 24.7 (cm²/m²), and 58% of patients were myopenic (table 1).

14 (27%) of patients experienced chemotherapy toxicity (grade 3 or 4 adverse event) within their first cycle. The toxicities included: 8 patients with neutropenia, 3 patients with infection, 2 with anorexia and 1 with diarrhoea (table 1).

Characteristic	Patients (N=52)
Male, n (%)	24 (47)
Age (years), median (IQR)	64.5 (56.8-73.0)
BMI (cm ² /m ²), median (IQR)	24.7 (21.3-27.4)
Myopenic, n (%)	38 (58)
Adverse events	
Toxicity, n (%)	14 (27)
Neutropenia, n (%)	8 (15)
Infection, n (%)	3 (6)
Anorexia, n (%)	2 (4)
Diarrhoea n (%)	1 (2)

Table 1: Demographics and chemotherapy toxicity
Abbreviations: Interquartile range (IQR), body mass index (BMI), number (n)
Myopenia is defined as muscle
Categorical variables presented as number with characteristic (percentage),
continuous variables presented as median (interquartile range).

Myopenia

Myopenia was not associated with an initial dose reduction ($p=0.2$), or chemotherapy toxicity ($p=0.06$) (table 2).

	Non-myopenic patients (n = 22)	Myopenic patients (n = 30)	p value
Initial dose reduction, n (%)	6 (27)	4 (13)	0.2
First cycle toxicity, n (%)	3 (14)	11 (37)	0.06
Table 2: Myopenia and chemotherapy Initial dose reduction refers to a gemcitabine dose per body surface area of $<1000\text{mg}/\text{m}^2$ or a nab-paclitaxel dose per body surface area of $<125\text{mg}/\text{m}^2$			

Neutrophil nadir and muscle

The neutrophil nadir following the first dose of gemcitabine nab-paclitaxel was associated with muscle attenuation ($R=0.31$, $p=0.03$) (figure 1B), but not skeletal muscle area ($R=0.04$, $p=0.79$) (figure 1A).

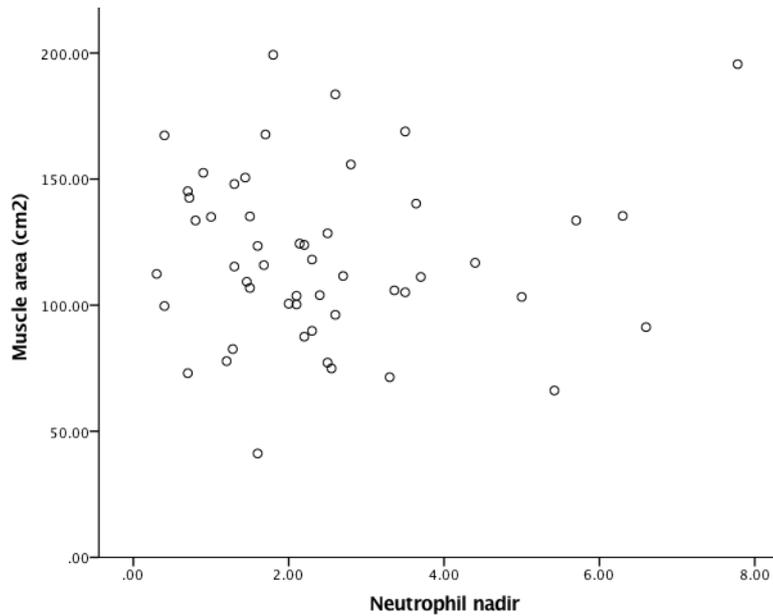


Figure 1A: Relationship between muscle area and neutrophil nadir (n=51).
 $R=0.04$, $p=0.79$.
 Pearson's rank correlation was used to determine significance or relationship between variables. Skeletal muscle area measured on single slice (L3) computed

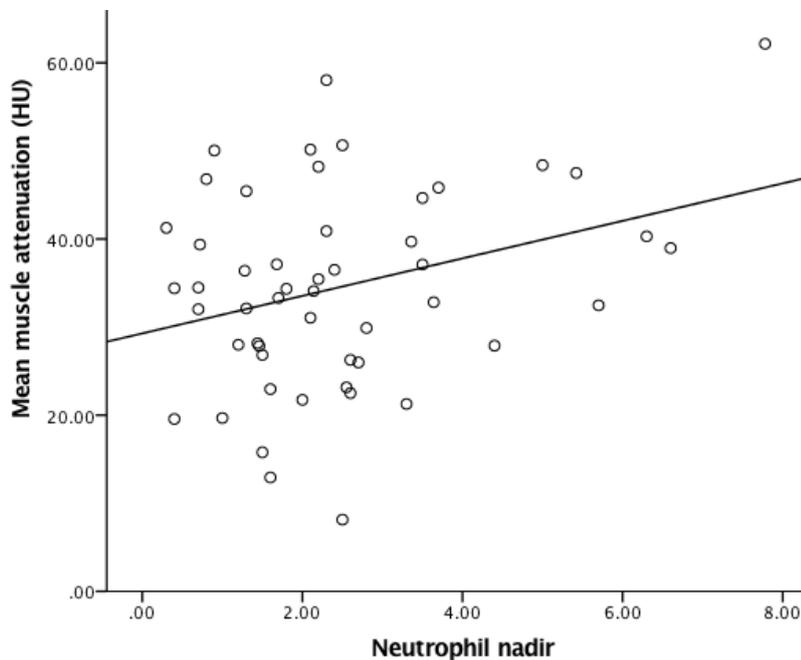


Figure 1B: Relationship between muscle attenuation and neutrophil nadir (n=51).
 $R=0.31$, $p=0.04$. Pearson's rank correlation was used to determine significance or relationship between variables. Skeletal muscle attenuation measured on single slice (L3) computed tomography scan is presented in Hounsfield units (HU).

Chemotherapy toxicity was not associated with skeletal muscle area, extramyocellular fat area or muscle attenuation (p=0.2, p=0.9 and p=0.8, respectively). Toxicity was also not associated with an increased gemcitabine dose to skeletal muscle ratio (p=0.8), nab-paclitaxel dose to skeletal muscle ratio (p=0.6) or combined gemcitabine and nab-paclitaxel dose to skeletal muscle ratio (p=0.9).

Body composition measurement	No toxicity (n=38), Median (IQR)	Toxicity (n=14), Median (IQR)	p value
VFA (cm ²)	135.4 (59.0-215.8)	93.9 (71.9-200.0)	0.8
SCFA (cm ²)	181.5 (106.0-236.7)	152.8 (99.1-207.9)	0.5
EMFA (cm ²)	7.6 (4.9-12.9)	9.0 (4.7-13.4)	0.9
SKMA (cm ²)	111.4 (98.0-137.9)	128.6 (91.9-140.9)	0.2
Muscle attenuation (HU)	35.0 (28.0-44.8)	32.2 (21.8-40.7)	0.8
Gemcitabine dose : skeletal muscle area (mg/cm ²)	14.4 (12.3-15.7)	14.1 (12.2-17.3)	0.8
Nab paclitaxel dose : skeletal muscle area (mg/cm ²)	1.8 (1.5-2.1)	1.8 (1.5-2.2)	0.6
CTx equivalent dose : skeletal muscle area (mg/cm ²)	2.9 (2.5-3.4)	2.8 (2.4-3.5)	0.9

Table 3: Body composition, chemotherapy dose and toxicity
Abbreviations: Interquartile range (IQR), visceral fat area (VFA), subcutaneous fat area (SCFA), extramyocellular fat area (EMFA), skeletal muscle area (SKMA), Hounsfield units (HU), chemotherapy (CTx)
Chemotherapy equivalent dose = (gemcitabine dose/1000) + (nab-paclitaxel dose/125) Kruskal-Wallis test was used to determine significance of relationship between variables.

Direct logistic regression was performed to assess the impact of muscle factors and chemotherapy doses on toxicity. The full model containing all predictors was statistically significant, $\chi^2 (5, N=52) = 11.9, p=0.037$ (table 4A), indicating that the model was able to distinguish between patients who had chemotherapy toxicity, and those who did not. As shown in table 4B, only one factor (gemcitabine dose) made a unique statistically significant contribution to the model, with an odds ratio of 1.01 ($p=0.27$).

	Chi-square	df	p value
Model	11.9	5	0.037

Table 4A: Omnibus test of model coefficients

	Exp (B)	Confidence interval for Exp (B)	p value
Muscle area (cm ²)	0.99	0.96 - 1.02	0.47
Muscle attenuation (HU)	0.95	0.88-1.02	0.17
EMFA (cm ²)	0.98	0.90-1.06	0.61
Gemcitabine dose (mg)	1.01	1.00-1.03	0.03
Nab-paclitaxel dose (mg)	0.92	0.84-1.00	0.052
Constant	0.03		0.27

Table 4B: Variables in the equation

Abbreviations: Hounsfield units (HU), extramyocellular fat area (EMFA)
 Logistic regression was performed to predict the impact of body composition and chemotherapy dose on likely hood of chemotherapy toxicity.

Discussion

PDAC is an aggressive malignancy, which is often diagnosed at a late stage due to the anatomical location of the pancreas. This means chemotherapy is most frequently given with palliative intent, which makes reducing chemotherapy toxicity in this group particularly important. Gem-Nab-P is a commonly used palliative regimen, proven to have improved survival over gemcitabine-alone.² It is, however, associated with significant toxicity, as demonstrated in the pivotal study by Von Hoff et al²⁰⁶, and in our study where 27% of the patients developed grade 3-4 toxicity within the first cycle.

This study was designed to examine the potential for optimising the dosing of Gem-Nab-P by adjusting BSA derived dose according to skeletal muscle mass, to reduce incidence of toxicity. In this section we used toxicity as a surrogate for excess dose, due to a lack of availability for testing of drug dose levels. We found no difference in body composition or drug dose to body composition ratio, between the no toxicity and toxicity groups. However, muscle attenuation (a measure of muscle quality), but not muscle area, was associated with the neutrophil nadir.

While this study was limited by a small sample size (n=52), the very close nature of the body composition and chemotherapy dose medians between the toxicity and no toxicity groups suggest that even if a much larger study was to achieve a statistically significant difference, it would be clinically insignificant. This was seen in the multi-variable analysis, where, while gemcitabine dose was identified as a statistically significant predictor of toxicity, the amplitude of the odds ratio made the difference clinically insignificant. For this reason, including muscle mass or other body

composition measures in the Gem-Nab-P dose equation is unlikely to reduce first cycle toxicity.

This study was also limited by its examination of only the first cycle of Gem-Nab-P treatment. It is possible that body composition has a different relationship with the toxicity that develops later in treatment. Particularly relevant for regimens involving nab-paclitaxel is the adverse event of neuropathy, which very rarely develops within the first cycle. It may be an endpoint in future research evaluating the role of body composition in longer-term chemotherapy toxicity.

As discussed, early serum levels of Gem-Nab-P cannot be measured. It is possible that neutrophil count could be used as a surrogate for drug levels. Our finding that neutrophil nadir is associated with muscle attenuation warrants further investigation. Amplitude of neutrophil count fluctuation is increasingly implicated in cancer outcomes, with chemotherapy-induced neutropenia associated with increased length of survival, compared to patients who do not experience chemotherapy-induced neutropenia.^{274, 275} It is possible that this could be further investigated using a more complete model of sarcopenia, involving muscle function as well as radiological measures.

We also demonstrated that myopenia at diagnosis was not associated with clinician decisions to initially dose reduce chemotherapy regimens. This is congruous with our finding that body composition, particularly muscle mass, is not associated with chemotherapy toxicity.

This study suggests that using body composition measures to alter BSA derived Gem-Nab-P is unlikely to result in reduced incidence of toxicity within the first treatment cycle. Further research is required to establish the

relationship between body composition, Gem-Nab-P dose and long-term toxicity.

We confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere. This research was not supported by any grants or other funding sources. The authors have no conflicts to declare. This study was approved by the Monash Health (Melbourne, Australia) Low Risk Human Ethics Committee, reference number: 16033L, and given site-specific approval at Eastern Health (Melbourne, Australia), reference number SERP09-2017.

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Conclusion

This study showed no relationship between the dose of Gem-Nab-P to skeletal muscle ratio and treatment toxicity, in the first cycle of Gem-Nab-P. This finding suggests that modifications to the current BSA-derived Gem-Nab-P dose by including a correction for skeletal muscle area are unlikely to result in a reduction of early treatment toxicity in PDAC patients. However, it is important to acknowledge that, while novel, this was one, small, retrospective study.

The study of pharmacokinetics using clinical outcome measures is imprecise. The strength of this type of study is that results have a direct clinical application. However, it does present interpretation difficulties, particularly in combination drug regimens. In this setting, gemcitabine is a hydrophilic drug, which means it distributes predominantly within lean tissue. Theoretically, this would mean that in patients with a sarcopenic obese phenotype, who would have a very high dose : skeletal muscle ratio, serum gemcitabine levels would be high, resulting in a greater number of dose related adverse events. However, the pharmacokinetics of nab-paclitaxel are less clear.

As the use of Gem-Nab-P continues to increase, there will be opportunity to study the effects of body composition on Gem-Nab-P pharmacokinetics and pharmacodynamics more thoroughly with the development of testing for Gem-Nab-P blood levels, which is not currently available. Also, further study of longer-term toxicity outcomes may demonstrate a different relationship to body composition in PDAC patients treated with Gem-Nab-P. This is important given the median time of onset of peripheral neuropathy, a significant toxicity associated with Gem-Nab-P, is 140 days (see chapter 2.3).

Given the poor prognosis of patients with locally advanced or metastatic PDAC who are treated with Gem-Nab-P, the reduction of adverse events to improve quantity and quality of life is essential. While this study produced negative results, we have presented a novel theoretical dosing experimental design, which could be applied to the study of other drugs with narrow therapeutic ranges.

5.2 The Malnutrition Screening Tool and myopenia

Introduction

At our institution, the Malnutrition Screening Tool (MST) is completed by nursing staff at each dose of chemotherapy for patients with PDAC. Patients who the tool identifies as at high risk of malnutrition are referred to the dietetics department for nutritional counselling. While this simple 'bed-side' tool allows for frequent monitoring of risk, we were concerned that two patient reported outcomes: weight loss and appetite, do not encompass the complexities of malnutrition and cancer cachexia syndrome, and therefore may miss patients who are in need of nutritional input, particularly in this very high risk cohort. Here we present the results of our investigation of the MST's efficacy at identifying patients with one element of this multifaceted syndrome, myopenia.

Background

Pancreatic ductal adenocarcinoma (PDAC) is associated with significant body mass, particularly lean body mass, loss. It has been well established that myopenic patients (patients with low muscle mass) have a poorer prognosis than non-myopenic patients with PDAC.^{1,2} It is not clear if this is secondary to weight loss itself, or the factors which cause loss of lean body mass. These factors include an aggressive tumour, high metastatic load and systemic inflammation, which result in the poor prognosis in this group. However, more accurately identifying myopenic patients would be useful for at least for prognosticating disease, and for targeting nutritional intervention.

The Malnutrition Screening Tool (MST) is a simple nutrition-screening tool based on two patient reported outcomes: unintentional weight loss and recent appetite. Patients with a maximum score of 2-5 points are thought to be at the higher risk of malnutrition than those with score of 0 or 1. The MST was developed in 1999 by Ferguson *et al.* to identify adult patients admitted for acute medical care who were at risk of malnutrition.³ The MST has since been validated as consistent with the 'gold standard' malnutrition risk test, the subjective global assessment, in cancer patients.⁴

The ability of the MST to identify the high-risk myopenic cancer patient group has never been examined. This study aims to characterise the relationship between MST score and myopenia in PDAC patients receiving chemotherapy.

Methods

This was a retrospective cohort study of 100 consecutive PDAC patients commencing their first dose of chemotherapy. Patients were identified using an ICD-10 coding search (C25: malignant neoplasm of the pancreas). Only patients who had a computed tomography (CT) scan involving spinal level L3 available, and who had chemotherapy treatment, were included in the study. A review of medical records was used to identify demographic information, disease information. MST scores were recorded by nursing staff at time of first dose of chemotherapy.

A single, experienced operator performed body composition analysis using SliceOmatic (TomoVision, USA) software. Muscle was identified by isolating tissue between -29 and +150 Hounsfield units (HU). Skeletal muscle index (SMI) was calculated using the formula $SMI = L3 \text{ skeletal muscle area (cm}^2\text{)} / \text{height (m)}^2$, and the SMI cut offs of <38.5 in women and <52.4 in men were used to define myopenia. These levels of muscle were determined to be significant in prognosis of pancreatic cancer by Prado *et al.* A body mass index of <20 kg/m² was defined as low and a serum albumin of <35 g/L was defined as low.

Fisher's exact test was used to determine significance of relationship between categorical variables and Mann-Whitney test was used for continuous variables. A p value of <0.05 was considered significant for all analyses.

This research was approved by the Monash Health Human Research Ethics Committee.

Results

	Not myopenic (n=53)	Myopenic (n=47)	p value
Age (years), median (IQR)	66 (57-71)	66 (55-72)	0.9
Sex (male), n (%)	19 (36)	28 (60)	0.02
Metastatic disease, n (%)	24 (45)	27 (57)	0.2
Low BMI, n (%)	3 (6)	7 (15)	0.1
Low albumin, n (%)	21 (40)	27 (57)	0.07
MST \geq 1, n (%)	31 (58)	27 (43)	0.5
MST \geq 2, n (%)	17 (32)	16 (34)	0.5
MST \geq 3, n (%)	12 (23)	6 (13)	0.2

Abbreviations: interquartile range (IQR), body mass index (BMI)

There were 100 patients (M 47%) included in this study, of which 47 were myopenic. Both the myopenic and the non-myopenic groups had a median age of 66 years. There was a significantly higher proportion of males in the myopenic group than the non-myopenic group (60% v 36, $p=0.02$). There was no significant difference in the prevalence of metastatic disease between the myopenic group and the non-myopenic group ($p=0.2$). In addition, there was no significant difference in the proportion of myopenic patients with a low BMI ($p=0.1$) or low albumin ($p=0.07$).

There was not a higher number of patients with an MST \geq 1 who were myopenic, compared to those who were not myopenic ($p=0.5$), nor were there a higher number of patients with an MST \geq 2 ($p=0.5$) or MST \geq 3 ($p=0.2$).

Discussion

We showed that patients with a MST score of 2 or above were not more likely to be myopenic than those with an MST score below two, when assessed at

commencement of chemotherapy for pancreatic cancer. We assessed different MST point cut offs, 1 and above, and 3 and above, but these scores also did not have a relationship with myopenia. This suggests that MST is an inadequate screening tool for identifying myopenic chemotherapy patients.

Interestingly, low BMI and low albumin levels also did not have a statistically significant relationship with myopenia in this cohort of 100 PDAC patients. While it is possible that a larger sample size may demonstrate a relationship, it is unlikely that these parameters, used in isolation, would be meaningful clinically as a screening tool for myopenia.

While myopenia is one important measure of nutritional status, it is important to acknowledge that there are a number of other nutritional parameters that our study did not assess including: rate of weight loss and lean body mass loss, transthyretin levels, micronutrients, functional status and quality of life.

Myopenia and malnutrition remain significant issues in patients receiving chemotherapy for PDAC, which often go unrecognised, particularly at early stages, by the healthcare system. Further research is required to develop sensitive and specific tools to identify patients who are, or who may be at risk of developing myopenia.

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Conclusion

The MST did not effectively identify myopenic PDAC patients at their first dose of chemotherapy. This suggests that using the MST at this time is likely to miss this at risk cohort who may benefit from dietetic intervention. It is important to acknowledge that myopenia is only one manifestation of malnutrition, and is contributed to by a range of other factors such as physical inactivity and systemic inflammation, which perhaps explains some of the difficulty identifying this patient group. However, given the strong association between cancer cachexia and PDAC, a more comprehensive screening tool, which is more sensitive to a wide spectrum of malnutrition and cachexia manifestations, may improve outcomes for PDAC patients.

Chapter 6: Conclusion

This thesis investigated the use of body composition to better understand the pathogenesis of, and to guide management of, inflammatory surgical diseases of the gastrointestinal tract.

Key findings

Firstly, this thesis explored the role of body composition and the metabolic syndrome in diverticular disease. It demonstrated that diverticulosis and diverticulitis are associated with a higher median VFA than controls. But there is no difference in VFA in patients with diverticulitis compared to patients with diverticulosis.

Based on the unexpected finding that there was no difference between the groups in the prevalence of T2DM, which is also inflammatory mediated, the thesis went on to explore the relationship between factors related to diabetes: glucose control and pharmacological management. This study demonstrated that metformin use was associated with a lower incidence of diverticulitis in a cohort of diabetics with diverticular disease. There was a trend towards a dose effect; higher doses of metformin were associated with diverticulosis, compared to diverticulitis.

Secondly, this thesis aimed to better describe the body composition phenotypes associated with localised and advanced pancreatic malignancies at the time of their diagnosis. In pancreatic ductal adenocarcinoma no difference in body composition was found between patients with metastatic and localised PDAC. However, in PNET patients, metastatic disease was

associated with significantly less fat, both visceral and subcutaneous, than in patients with localised disease. In both pancreatic malignancies size of the primary pancreatic tumour was not associated with body composition parameters.

This thesis proceeded went on to examine more thoroughly the functional status of patients at the point of diagnosis of pancreatic ductal adenocarcinoma. A large prospective study found that anorexia and related symptoms are prevalent around the time of diagnosis of pancreatic ductal adenocarcinoma. In terms of muscle function in pancreatic ductal adenocarcinoma, peak expiratory flow strongly correlated with handgrip strength, without any significant outliers. Peak expiratory flow was significantly reduced in sarcopenic patients compared to non-sarcopenic. Both muscle size and muscle quality were associated with handgrip strength, but could not fully predict handgrip strength.

Finally, this thesis sought to examine the clinical utility of body composition measurement in the management of patients with pancreatic ductal adenocarcinoma. It demonstrated that gemcitabine nab-paclitaxel toxicity was not associated with dose to skeletal muscle index ratio. This suggests that variation of dosing according to individual body composition phenotype in this regimen may not result in reduced toxicity. However, muscle attenuation positively correlated with neutrophil nadir; poor muscle quality was associated with lower day 7-14 nadirs. There was no difference in Malnutrition Screening Tool score between myopenic and non-myopenic patients with pancreatic ductal adenocarcinoma.

Implications and significance of this research

The third chapter of this thesis, in the context of other consistent research in this area, establishes a firm association between diverticular disease and increased levels of visceral adipose tissue. It is feasible that when present in excess this association can be explained by visceral adipose tissue creating a pro-inflammatory environment in the colon, which propagates diverticular disease in susceptible individuals. Perhaps, by reducing visceral adipose tissue, through lifestyle and pharmacological intervention, the incidence of, and the severity of this common and potentially fatal disease, could be mitigated. This thesis also presents the novel use of metformin in diverticular disease. Given the lack of effective therapeutic options for diverticular disease this is an exciting prospect, and presents an enticing avenue for future work.

The investigation of body composition in non-functioning PNET was novel, and contributes to the relative paucity of literature surrounding these increasingly common tumours. Chapter three also contributes to a more complete understanding of the functional status of PDAC patients around the time of the diagnosis of disease. This thesis provides contemporary data that describes the prevalence of myopenia and sarcopenia, as well as symptoms that may contribute to weight loss. The high prevalence of these symptoms suggests that aggressive nutritional and symptom management interventions implemented at the time of diagnosis of PDAC may be beneficial for a majority of patients, and that the effectiveness of this kind of early intervention certainly warrants further investigation.

The final part of this thesis was designed to investigate the potential for body composition analysis to be used to personalise and improve the treatment of

patients with pancreatic ductal adenocarcinoma. Firstly, it aimed to investigate the inclusion of skeletal muscle area into the traditional body surface area dosing equation of gemcitabine nab paclitaxel. While previous studies have suggested that alterations of body composition phenotype within any given BSA may alter chemotherapy volume of distribution, notably 5-fluorouracil, also used in pancreatic cancer, the study within the thesis did not demonstrate the same trends for gemcitabine nab paclitaxel. The pharmacokinetic theory underlying this study has been discussed throughout this thesis. This experimental design may well be able to be applied to other drugs with narrow therapeutic ranges to investigate the relationship between varying body composition phenotype and volume of distribution.

Limitations of research and avenues for future research

This thesis presents preliminary work defining body composition phenotypes associated with gastrointestinal disease states.

Difficulty developing control groups free of selection bias limited the diverticular disease and body composition study (chapter 3). While efforts were made to select 'healthy' controls, representative of the general population, the requirement for cross-sectional imaging to have been performed introduced the potential for confounding. Again in chapter 3, the metformin study was limited by the availability of a control group. Hospital admission records were used to identify patients. As diverticulosis is an asymptomatic condition, these patients had another indication for interaction with the health system, possibly confounding results. Given metformin's negligible side effect profile (in appropriately selected patients), prospective

interventional research would be an appropriate next step in investigating its potential utility in diverticular disease outcomes such as the incidence of diverticulitis, colonic inflammation and gut flora modulation.

The results of this thesis are derived from retrospective and cross-sectional research, which, by design, cannot distinguish between causation and effect. Throughout the thesis, suggestions have been made as to the pathways that may explain the relationships that have been described. However, this research can only act as a framework, on which further research can be built, to work towards gaining full understanding of the complex interplay between body composition, inflammation and disease. Prospective research, which examines body composition longitudinally throughout the course of these diseases, may aid in elucidating cause and effect relationships between these diseases and body composition.

Due to their relative rarity, the sample populations presented in the PNET body composition study (chapter 4), and the Gem-Nab-P toxicity study (chapter 5), were small. As discussed in each chapter, while some clinically meaningful results could be extrapolated from these groups, larger sample sizes may identify relationships that are too subtle to be identified by our work. It would also allow for subgroup analysis.

While the study of Gem-Nab-P was designed intentionally to study a key emerging regimen used for palliative management of pancreatic cancer, in a way that provided results directly applicable to clinical practice, its design did limit the potential of the study to elucidate the relationship fully between body composition and pharmacokinetics. A study of a regimen that involves two chemotherapy agents given simultaneously excludes the ability to definitively attribute adverse events to either agent. It therefore limits our

ability to extrapolate the results to more fully understand the relationship between body composition and Gem-Nab-P pharmacokinetics.

The final study presented is limited by its scope. It presents a probative finding that MST score is not associated with myopenia in the patient group studied; it does not evaluate all aspects of its clinical utility. While there is a temptation to rely on objective physiological outcomes, meaningful analysis of nutritional tools requires a holistic approach.

Summary

Body composition analysis is a useful tool to improve the understanding of, and possibly the management of, disease of the gastrointestinal tract. There is an association between a body composition phenotype high in visceral adipose tissue and diverticular disease. Metformin may have the potential to partly mitigate risk of diverticulitis in these patients. The interplay between body composition and pancreatic cancer is complex. Loss of muscle volume is associated with a proportional loss of muscle strength. There is a high prevalence of myopenia and sarcopenia at diagnosis of PDAC, as well as a high prevalence of symptoms associated with anorexia. Dosage of Gem-Nab-P to skeletal muscle area is not associated with toxicity in PDAC. The MST does not effectively identify myopenic PDAC patients at commencement of chemotherapy.