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Fecal elastase, an assay for exocrine pancreatic insufficiency, has clinical utility in patients with pancreatic ductal adenocarcinoma

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Dear Editor,

Pancreatic cancer-associated weight loss (PAWL) is a multifactorial syndrome that can be attributed to anorexia, malabsorption/exocrine pancreatic insufficiency (EPI), and cachexia.[1] The precise mechanisms driving PAWL are poorly understood. Recent pre-clinical work employing pancreatic ductal adenocarcinoma (PDAC) mouse models with $Kras^{G12D}$ activation suggested that adipose and skeletal tissue wasting occurred as an early event when pancreatic tissue weight was unchanged and before the onset of cancer.[2] While endocrine pancreatic function did not appear to be affected in early PDAC, decreased exocrine pancreatic function appeared to mediate adipose tissue loss as evidenced by higher fecal lipids, decreased fecal protease activity, and increased fecal protein content in PDAC mice compared with control mice. Pancreatic enzyme replacement therapy (PERT) mitigated the degree of adipose tissue wasting in PDAC mice further establishing the role of decreased exocrine pancreatic function in promoting peripheral tissue wasting in early PDAC.

Given that PDAC-associated cachexia may represent an early event that is putatively driven by altered exocrine function, we sought to investigate the relationship between impaired exocrine pancreatic function as measured by fecal elastase and PAWL in PDAC, which has been largely unexplored in the clinical setting. We evaluated the diagnostic and predictive utility of fecal elastase, a stool assay that evaluates exocrine pancreatic function even with simultaneous enzyme supplementation,[3,4] for PAWL in an Institutional Review Board (IRB)-approved (Pro00056515) cohort of PDAC patients upon diagnosis at our institution. Fecal elastase was measured in solid stool, to avoid dilution and false-positive results. Specifically, we defined PAWL as clinically significant weight loss in patients with PDAC who had unintentional weight loss >5% over 6 months preceding diagnosis that fulfilled a consensus definition of cachexia.[1] We used a historic criterion for low fecal elastase (<200 μg/g), which has been shown to be fairly sensitive for EPI although a high rate of false positives can occur.[4–6] Clinical variables were abstracted from each subject's electronic medical record.

A total of 38 consecutive subjects had stool specimens collected for fecal elastase after diagnosis of PDAC and at initial consultation in our gastrointestinal medical oncology clinic; none had undergone any pancreatic surgery at the time of collection. The median age was 70 (range 47–96 years), 58% were male, 60% were stage III–IV (American Joint Committee on Cancer), and 71% had low fecal elastase. The mean fecal elastase level was 89.1 and 330.8 μg/g in those with and without clinically significant weight loss, respectively. Of the 28 subjects with low fecal elastase, 68% did not have other overt symptoms (diarrhea, steatorrhea, or change in stool character) of EPI although 93% experienced some weight loss. Of the 10 subjects with normal fecal elastase, 70% did not have other overt symptoms of EPI although 40% experienced some weight loss.

The performance of the fecal elastase assay was fairly sensitive (86.7%) and specific (75%) for PAWL in our PDAC cohort. Interestingly, in a separate cohort of eight patients with pancreatic neuroendocrine tumors (PanNETs), all had normal fecal elastase (average 403.9 μg/g) and none had clinically significant weight loss, whereas

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virtually 80% of subjects in our PDAC cohort had clinically significant PAWL at diagnosis. Furthermore, review of imaging at the time of diagnosis and collection of fecal elastase in our PDAC cohort identified that of those with low fecal elastase, 82% had pancreatic head masses, 93% had associated pancreatic ductal dilation, and 86% had associated gland atrophy.

Although EPI has been classically associated with pancreatic disorders including malignancy, weight loss develops late in the course of EPI when pancreatic lipase secretion is <10% of normal.[7] Our findings support that fecal elastase may be an early and sensitive assay to identify EPI and PAWL even in the absence of a high index of clinical suspicion for EPI, which warrants further investigation. This ability is provocative in order to identify PDAC patients, at an earlier stage, who could benefit from the multidisciplinary optimization of nutritional status inclusive of strategies such as PERT, which has translated into positive advances in patient quality of life and outcomes in pancreatic cancer.[1]

We have now routinely incorporated baseline fecal elastase measurements as part of our multidisciplinary care for newly diagnosed PDAC patients to further direct management of weight loss according to consensus recommendations.[1] For example, all patients with PAWL and low fecal elastase in our cohort were referred for nutritional counseling by a registered dietitian nutritionist, nearly all were started on PERT (82%), and several patients met criteria for enrollment in clinical studies investigating body composition measurements by various imaging modalities and/or enteral nutrition in optimizing nutritional status and improving weight loss.

Intriguingly, we collected fecal elastase in eight patients with PanNETs and discovered that all had normal fecal elastase at baseline and none had clinically significant weight loss. In mice models, pancreatic tumor growth was shown to be the primary contributor of early adipose tissue wasting.[2] However, our findings suggest that not all pancreatic tumors may drive the EPI-associated PAWL phenotype. PanNETs arise from a different cell of origin and have historically been less associated with weight loss, pancreatic ductal dilation, and arterial invasion than other solid pancreatic neoplasms.[8] In our cohort, imaging review corroborated that patients with PDAC tumors located to the head, having associated pancreatic ductal dilation, and having pancreatic atrophy comprised the majority of those with low fecal elastase, while the majority of those with normal fecal elastase had non-head pancreatic tumors, no ductal dilation, and no pancreatic atrophy. We present hypothesis-generating findings that the PAWL phenotype is not solely dependent on the occurrence of any pancreatic tumor, but rather may be associated with anatomic and biologic features intrinsic to the neoplastic cell of origin that warrants further investigation to better understand, detect, and manage PAWL.

Author contributions

Study concept and design: J.G., A.H.; acquisition of data: J.G., M.G., V.H.; analysis and interpretation of data: J.G., A.H., C.F., M.P.; drafting of manuscript: J.G.; critical revision of the manuscript for important intellectual content: all authors.

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