Evaluating Steatosis in Pancreatic Transplant

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Abstract

Pancreatic transplant remains the only treatment that cures insulin-dependent diabetes mellitus. It is recognized by transplant surgeons that donor pancreases with excessive fat infiltration have a poorer clinical outcome, resulting in significant recipient morbidity and mortality. However, no objective measure of pancreatic fat infiltration exists, and no study has been done that correlates the level of fat infiltration with clinical outcome. There have been significant radiologic advances that allow assessment of fat content of organs, and these could be used to accurately quantify the extent of pancreatic fat infiltration. We reviewed the literature regarding pancreatic steatosis, and examined ways in which the level of steatosis could be objectively measured before transplant, thereby improving clinical outcome.

Key words: Pancreas, Graft, Fat, Diabetes, Surgery

Introduction

Transplant surgeons have noted that a pancreas visibly infiltrated by fat (Figure 1) at retrieval tends to have a much poorer clinical outcome. Pancreases that are deemed to have excessive fatty infiltration (Figure 2A and 2B) are not used. Yet this assessment is made by simply “eye-balling” the pancreas and assessing macroscopic evidence of fat infiltration; not by any objective measure. Hence, we sought to explore the phenomenon of pancreatic steatosis.
(fatty infiltration of the pancreas) and its implications for organ transplant. Ultimately, we wish to suggest ways to translate this clinical observation into objective measures that can be used to predict and improve clinical outcome.

Ogilvie\(^1\) first described pancreatic steatosis in 1933, when he noted an association between fatty infiltration of the pancreas and obesity: obese cadavers had 17% pancreatic fat, while lean cadavers had only 9% fat. This finding was confirmed by subsequent radiologic studies using endoscopic ultrasound,\(^2\) computed topography\(^3\) and magnetic resonance spectroscopy,\(^4\) which demonstrated that pancreatic steatosis increases with body mass index. Other factors associated with increased pancreatic fat infiltration include age,\(^5\) type 2 diabetes mellitus,\(^4\) hepatic steatosis\(^2\) and alcohol use.\(^2\)

Pancreatic steatosis has significant clinical implications for transplant. Fat accumulation in the pancreas predisposes to acute pancreatitis with a more severe clinical course,\(^6\) as well as to chronic pancreatitis.\(^7\) Risk factors for graft pancreatitis include donor age\(^8\) and obesity,\(^9\) which themselves are risk factors for pancreatic steatosis. Graft pancreatitis and donor age are also independent risk factors for vascular thrombosis.\(^10\) This is the most common surgical complication post-transplant, with an incidence between 3% and 10%,\(^11\) and is the leading cause of technical failure.\(^10\) If prompt laparotomy is not performed, then graft thrombosis leads to other complications that significantly affect patient morbidity and mortality.\(^12\) Other clinical implications of pancreatic steatosis include an increased incidence of postoperative pancreatic fistulae\(^13\) and pancreatic cancer.\(^7\)

Pancreatic transplant remains the only treatment that normalizes glucose metabolism in patients with insulin-dependent diabetes mellitus; in fact, normoglycemia is usually established within minutes after reperfusion. Significant strides have been made since December 17th, 1966, when the world’s first clinical pancreas transplant was performed at the University of Minnesota Hospital in the United States.\(^14\) Therefore, we must make every effort to improve this treatment, given that it is our only hope of curing insulin-dependent diabetes mellitus.

**Clinical overview of pancreatic steatosis**

**Predisposing factors**

Pancreatic steatosis is associated with body mass index. Lingvay and associates\(^4\) demonstrated that magnetic resonance spectroscopic measurement of human pancreatic triglyceride content increases with body mass index. This was reflected in work by Al-Haddad and associates,\(^2\) who showed that patients with hyperechogenicity of the pancreas (a marker of steatosis) had significantly higher median body mass indexes than did patients without it. Aging also predisposes the pancreas to steatosis.\(^5\)

Impaired glycemia is related to pancreatic steatosis. Patients have been shown to have more fat infiltration of the pancreas on magnetic resonance spectroscopy if they had impaired fasting glucose/impaired glucose tolerance, or type 2 diabetes mellitus, than if they were normoglycaemic.\(^4\)

Studies also show an association between a high fat diet and adipocyte infiltration of pancreatic tissue both in humans and mice.\(^15\) In humans, we know that changes in composition of dietary fatty acids cause alterations in the pancreatic fatty acid composition.\(^15\) However, malnutrition also increases pancreatic steatosis.\(^16\) Work by Chehter and associates\(^17\) corroborates this finding: they showed that AIDS patients had an accumulation of lipid droplets in the pancreas, which may be a result of malnutrition and/or the HIV itself.

Alcohol intake also closely correlates with pancreatic steatosis. Al-Haddad and associates\(^2\) demonstrated that patients with an alcohol intake of more than 14 grams/week had significantly more pancreatic hyperechogenicity than those with a lower alcohol intake. This fact was reflected in a study by Lopez and associates,\(^16\) in which 3 months of ethanol consumption by rats increased their pancreatic cholesterol ester content.

Steatosis of other organs may contribute to the development of pancreatic steatosis. Hepatic steatosis is a strong predictor of a hyperechogenic pancreas, with an odds ratio of nearly fourteen.\(^2\) Other associations of pancreatic steatosis include cystic fibrosis\(^18\) and leptin deficiency.\(^19, 20\)

**Clinical implications for transplant**

Pancreatic steatosis exacerbates the severity of acute pancreatitis\(^6, 7\) and promotes chronic pancreatitis.\(^7\)
Obese leptin-deficient mice were found to have more intralobular and interlobular pancreatic fat on histology, with significantly more TNF-α and IL-1β in their pancreases. These mice had intraperitoneal saline or caerulein injections to produce edematous pancreatitis: the obese mice had more severe pancreatitis on histology than did the lean mice. The risk factors for graft pancreatitis (Figure 3) include donor age and obesity. There is also a well-documented association between both donor age and body mass index with pancreatic steatosis. Donor age and graft pancreatitis are themselves risk factors for graft thrombosis. Thrombosis accounts for 70% of all technical failures and invariably results in graft loss, relaparotomy and transplant pancreatectomy. Grafts from older donors have higher rates of thrombosis, graft loss and patient mortality. Older donor age and graft pancreatitis also are risk factors for intra-abdominal infections after surgery, which can result in high rates of graft loss and patient mortality.

Delayed endocrine graft function is defined as the need for transient insulin administration during the early postoperative period, and donor age over 45 years is a risk factor for this.

Pancreatic steatosis also increases the risk of postoperative pancreatic fistula: patients who developed a pancreatic fistula had significantly more interlobular, intralobular and total pancreatic fat.

Pancreatic cancer is strongly associated with obesity. Patients with pancreatic cancer are more likely to have a high body mass index, consume high fat and saturated fat diets and have diabetes. Mathur and associates found that increased pancreatic fat was related to increased dissemination and lethality of pancreatic cancer.

Patients were found to have significantly more fat cells in their pancreases, and a reduced mean survival as compared with node-negative patients (approximately 19 months compared with 31 months). Pancreatic steatosis also closely correlates with obesity, impaired glucose tolerance and diabetes.

**Radiologic assessment of pancreatic steatosis**

**Endoscopic ultrasound**

Hyperechogenicity of the pancreas, which is readily seen on endoscopic ultrasound, suggests the pancreas is infiltrated with fat. The proximity of the ultrasound probe to the pancreas gives a high spatial resolution that is superior to that given by computed topography or magnetic resonance imaging. Ultrasound reveals steatosis owing to its increased parenchymal reflectivity.

**Computed topography**

Fatty infiltration of the pancreas is readily identifiable on computed topography both with and without intravenous contrast. It appears as a separation of the parenchymal tissue by fat, which accentuates the appearance of pancreatic lobules. This fatty infiltration can be uniform or uneven throughout the pancreas. Computed topography works by measuring tissue attenuation. Contrast-enhanced computed topography provides high spatial and temporal resolution compared with magnetic resonance imaging; however, it also exposes the patient to radiation and nephrotoxicity from iodinated contrast agents.

**Magnetic resonance spectroscopy**

Magnetic resonance imaging does not use ionizing radiation, and gadolinium-diethylenetriamine pentaacetic acid is well tolerated and not nephrotoxic, so it can be used in renal-compromised patients. Several magnetic resonance imaging methods are capable of assessing the fat content of tissues. The method that assesses the frequency shift between water and fat resonances is most commonly used.

The Dixon method exploits the chemical shift difference between protons in water and fat, thus leading to water-selective and fat-selective images. However, the results can be affected by T1- and T2-relaxation effects. The spectral-spatial excitation method combines chemical shift selectivity with
slice-selective excitation. This technique has a high sensitivity and therefore is particularly good for small amounts of fat.

A recently developed method—Iterative Decomposition with Echo Asymmetry and Least square estimation (IDEAL)—is a fat-water 3-dimensional technique, which produces separated fat and water images optimal in signal-noise ratio. It acquires 4 images, and each has a different relative phase between the fat and water signals. The echo times of the 4 images are chosen carefully to ensure that the highest signal-noise ratio is achieved in the reconstructed fat-only and water-only images.

Studies have shown IDEAL is superior to single-voxel magnetic resonance spectroscopy, which is currently the criterion standard noninvasive technique for fat quantification and is routinely used to measure liver steatosis. Magnetic resonance spectroscopy methods have been validated for quantifying pancreatic steatosis—magnetic resonance spectroscopy-based measurement of pancreatic triglyceride content accurately correlated with biochemical assays in lean, obese, and diabetic rodents. Magnetic resonance spectroscopy also detects differences in pancreatic triglyceride content in humans ranging from lean to obese, and demonstrates intrasubject reproducibility. IDEAL captures images during breath-holding intervals and, compared with single-voxel magnetic resonance spectroscopy, is less susceptible to respiratory motion effects. It provides greater spatial resolution and anatomic detail than single-voxel magnetic resonance spectroscopy; therefore IDEAL can more accurately assess the fat content of smaller organs such as the pancreas.

IDEAL imaging allows reliable and uniform fat suppression throughout the body, including the abdomen, pelvis, extremities, head and neck, breast and heart. Moreover, this fat suppression is standardized between patients and between technicians. IDEAL offers another advantage in that all images (in-phase, opposed-phase, fat-only and water-only images) are obtained during a single acquisition, and therefore allows simplification of magnetic resonance imaging protocols and shorter scan times. IDEAL is also cost-effective, as it is simply a pulse sequence that can be added to an existing magnetic resonance imaging protocol. The use of IDEAL is compatible with essentially any pulse sequence, including fast spin echo and steady-state free precession. As a result of this, fat- and water-separated images can be produced with any contrast (T1-weighted, T2-weighted, and proton density-weighted images), with motion compensation, with 2-D or 3-D acquisitions, and use of contrast media.

Discussion

Risk factors for pancreatic steatosis include an increased body mass index and advancing donor age. Pancreatic steatosis is a predisposing factor for pancreatitis. Recipients are at a higher risk of graft pancreatitis if the donor is older or obese. One can extrapolate that pancreases from older donors with higher body mass indexes have more steatosis, and this predisposes them to graft pancreatitis.

Increasing donor age and graft pancreatitis are risk factors for graft thrombosis and intra-abdominal infections. Grafts from older donors and those that become infected have a higher graft loss rate and a higher recipient mortality rate. Pancreases from older donors and those that develop graft pancreatitis are at an increased risk of thrombosis and infection, probably as a result of increased steatosis. The graft also may display delayed endocrine function with advancing donor age.

Obesity and diabetes are risk factors for pancreatic cancer and lead to increased dissemination and lethality of pancreatic cancer. Pancreatic steatosis is closely associated with obesity, impaired glucose tolerance and diabetes, and may be the intermediary link correlating obesity and diabetes with pancreatic cancer. It is clearly not in the best interest of the patient to transplant a pancreas that is at high risk of developing cancer. More work must be undertaken to understand whether steatosis is the link between age/obesity and increased risk and lethality of pancreatic cancer. Pancreatic steatosis itself is a direct risk factor for postoperative pancreatic fistula, which is obviously an undesired outcome of transplant surgery.

It is evident that pancreatic steatosis is associated with significant ill effects on the graft and thereby the recipient. Hence, it is no longer acceptable for the assessment of fat accumulation to be based on the pancreas' appearance at retrieval. We must be able to quantify the amount of fat infiltrating the pancreas, and need to further study the clinical outcome of pancreatic steatosis. There have been significant
radiologic advances which allow assessment of the fat content of organs, and these could be used to quantify pancreatic fat in an organ considered for transplant.

Though endoscopic ultrasound has shown good results, it is not sufficiently accurate for fat quantification in the pancreas. Computed topography methods do not detect hemosiderin deposition and other histologic changes in the pancreas that result in anomalous elevations in tissue attenuation. Computed topography also involves radiation exposure and potential nephrotoxicity from iodinated contrasts.

Magnetic resonance imaging, conversely, does not use ionizing radiation and gadolinium-diethylenetriamine penta-acetic acid is well tolerated and non-nephrotoxic. Magnetic resonance imaging has been shown to be useful in correcting misdiagnosis from ultrasound and computed topography in focal steatosis. There are multiple magnetic resonance imaging techniques for quantifying the fat content of organs, and the current noninvasive criterion standard is single-voxel magnetic resonance spectroscopy, which is routinely used to measure liver steatosis. Magnetic resonance spectroscopy methods have been validated for quantification of pancreatic steatosis.

IDEAL is a newer, 3-dimensional technique, that produces separated fat and water images with optimal signal-noise ratios. It captures images during breath-holding intervals, and it is much less susceptible to respiratory motion effects compared with single-voxel magnetic resonance spectroscopy. It provides greater spatial resolution and anatomic detail than single-voxel magnetic resonance spectroscopy, and so can more accurately assess fat content of smaller organs such as the pancreas. IDEAL imaging allows reliable standardized fat suppression throughout the body, including the abdomen, and all images (in-phase, opposed-phase, fat-only, and water-only images) are obtained during a single acquisition. This allows simplification of magnetic resonance imaging protocols and therefore shorter scan times. The use of IDEAL is cost-effective, as it is compatible with essentially any pulse sequence and can be added to an existing magnetic resonance imaging protocol.

One could postulate that there are two opportunities for the pancreas to be radiologically assessed before transplant—before and after retrieval. Before retrieval would involve performing a scan on the deceased/dying donor, which could understandably cause distress to the donor and their family. Scanning the organ after retrieval is more feasible given the short time required for magnetic resonance imaging scans. IDEAL scanning requires breath-holding intervals; therefore, the implication of this on scanning a sole organ must be assessed further.

Pancreas transplant remains the only option for curing insulin-dependent diabetics. However, despite this potentially large recipient pool, the widespread application of pancreas transplant has been hindered by the significant rate of surgical complications resulting in graft failure/loss and, more importantly, recipient morbidity and mortality. Pancreatic steatosis may be a contributing factor to this high rate of surgical complications. Hence, it must be properly assessed and quantified in potential donors to ensure that only optimal quality grafts are transplanted. This would considerably improve the chances of a successful outcome for the recipient. Eventually, we should aim towards a system of determining an acceptable level of fat accumulation in a given pancreas, to assess its suitability for transplant.

References

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