Received: 2 September 2022 | Revised: 22 December 2022 | Accepted: 29 December 2022

DOI: 10.1111/ctr.14899

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

REVIEW ARTICLE

Comprehensive review: Frailty in pancreas transplant candidates and recipients

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Abstract

Well-selected patients with kidney disease and diabetes mellitus who undergo simultaneous kidney-pancreas transplantation often experience dramatic improvements in quality of life and long-term survival compared to those who remain on medical therapy. Over the past several years the importance of frailty in the pancreas transplant candidate and recipient populations has grown. More patients with advanced age have entered the waitlist, and complications from prolonged diabetes, even in younger patients, have created increased evidence of risk for frailty. Given these concerns, and the broad challenges facing pancreas transplantation volumes overall, we generated this review to help establish the impact and implications. We summarize the interplay of immunological factors, aging, environmental factors, diabetes mellitus, and chronic kidney disease that put these patients at risk for frailty. We discuss its measurement and recommend a combination of two instruments (both well-validated and one entirely objective). We describe the outcomes for patients before and after pancreas transplantation who may have frailty, and what interventions can be taken to mitigate its effects. Broader investigation into frailty in the pancreas transplant population is needed to better understand how to select patients for pancreas transplantation and to how manage its consequences thereafter.

KEYWORDS
frailty, pancreas after kidney transplantation, pancreas transplant alone, pancreas transplantation, simultaneous pancreas-kidney transplantation, type 1 diabetes mellitus, type 2 diabetes mellitus

1 | INTRODUCTION

Frailty is an age-related condition of physiological decline characterized by vulnerability to adverse health outcomes.[1] The term is relatively new to the field of transplantation, initially characterized mostly in liver, heart, and lung transplantation, and more recently in kidney transplantation.[2–4] Frailty is a holistic, broad, multidimensional term, which readers should be careful to distinguish from other related

findings, such as sarcopenia, which refers specifically to muscle loss and may be coincident with frailty, but the two terms are not synonymous.[5] Frailty may be assigned in a binary fashion, but is better thought of along continuum of patient health and function. While scoring systems have been devised to define frailty, often an exact threshold is ephemeral and temporally dependent. In this review we will consider scoring systems "validated" when they have been studied sufficiently to reach a level of relative acceptance from a community of investigators.

Frailty is common in patients with diabetes mellitus (DM), chronic kidney disease (CKD), and end-stage kidney disease (ESKD).[6] The increased prevalence of frailty in the CKD population is likely a result of the aging population in the United States, coupled with the growing epidemic of DM.[7] The Fried Frailty Phenotype (FFP) score is a validated tool that characterizes the degree of frailty according to five components: two objectively measured (weakness via grip strength and slowness via timed walk) and three subjectively measured through patient report (exhaustion, low physical activity, and unintentional weight loss), wherein a score ≥ 3 is considered frail.[8] Another important tool in frailty measurement is the short physical performance battery (SPPB) that is a well-validated, objective measure of lower extremity function which has been shown to predict a 2.3-fold increased risk of mortality after kidney transplantation.[9,10] Clinicians often use the term "functional status" during the discussion of frailty, which is measured using the Karnofsky Performance Score (KPS) when they provide their estimate of the patient's capacity for activity before transplantation. Patients with frailty can also have "cumulative deficits" which need to be considered. A frailty diagnosis requires the provider to investigate the patient's collective medical/social history, physical exam, and imaging, as well as appreciation that its detection can be challenging, malleable, and intervened upon in many cases.

Pancreas transplantation (PTx) is an excellent therapy, offering the best short-term and long-term treatment option for patients with labile, insulin-dependent DM.[11,12] In the absence of transplantation, patients are at elevated risk for secondary complications of DM such as retinopathy, neuropathy, gastroparesis, and nephropathy, which may culminate in premature death.[13] PTx changes the health trajectory of patients with DM as its accumulated effects and secondary complications can be slowed by simultaneous pancreas-kidney transplantation (SPK) with reversal of microvascular damage.[14,15] Importantly, however, the profile of potential PTx candidates/recipients has changed and is now somewhat older, which increases the risk for frailty.[16] Indeed, compared with patients who presented for PTx in 2008, more patients (10.1%) who presented in 2020 were more likely to be older than age 55.[17,18] In 2017, 27% of PTx waitlisted candidates were older than 50, and 3% were older than 60.[19]

Also, although waiting times for PTx (typically <2 years) are relatively short compared to isolated kidney transplant (often at least 4–8 years for most blood groups), SPK candidates may present with frailty, necessitating the consideration for therapeutic intervention.[20] As an example, sarcopenia and osteoporosis, both of which have been used as surrogates for frailty in the literature, are frequent complications in adults with type 1 DM.[21] Further, patient with type 2 DM display greater rates of skeletal fragility.[22] Given the frequency of DM + ESKD in the PTx candidate pool, frailty may serve as a major mortality risk factor in PTx candidates and recipients.[23,24]

To synthesize the current state of knowledge of frailty in PTx, the Pancreas Workgroup of the American Society of Transplantation (AST) Kidney Pancreas Community of Practice (KPCOP) performed a comprehensive literature review. We have a broad authorship to embrace to diversity of perception and experience related to frailty in pancreas transplantation across the United States. Our goals were to (1) summarize the pathogenesis of frailty as it relates to PTx candidates, (2) recommend the best instruments for frailty measurement in PTx candidates, (3) describe the impact of frailty surrogates on PTx waitlist candidates, (4) PTx outcomes, and (5) provide strategies to potentially mitigate frailty and improve PTx outcomes. This manuscript is a work product of the American Society of Transplantation's Kidney Pancreas Community of Practice.

1.1 | Review methodology

We performed a comprehensive literature review of Embase, PubMed, Google Scholar, Ovid Medline, Web of Science, and Cochrane for articles published from January 1, 2000 to December 20, 2022 related to frailty and PTx written in English with the following search terms: simultaneous pancreas kidney transplant/ transplantation, pancreas transplant/transplantation and frailty, frailties, frailness, frailty syndrome, debility, or debilities. Review of those articles was performed to evaluate and determine additional relevant articles. We considered authors who defined frailty according to the Fried Frailty Phenotype, although we did consider other measurements of alternative tests for frailty.

2 | PATHOGENESIS OF FRAILTY IN DIABETIC CHRONIC KIDNEY DISEASE

Diabetes mellitus is a disabling chronic condition associated with cardiovascular, peripheral vascular, and chronic kidney diseases.[25–27] DM can be a major medical and social burden due to frequent clinic visits, blood work, and intensive monitoring. Further, there is emotional stigma from "being diabetic" that is frequently underreported, but which causes patient harm.[28] For these reasons, frailty is believed to be common among the PTx candidate population.[29] Frailty in patients with chronic kidney disease and kidney transplantation has been previously reviewed,[30] which has many of the same biological, environmental, and social determinates of health as pancreas transplant candidates.

Much of the current relevant data regarding frailty in PTx patients come from the type 1 DM literature in the pre-transplantation phase. Maratova et al. noted in related conditions that sarcopenia and osteoporosis are late complications of type 1 DM in adults and that type 1 DM negatively impacts the musculoskeletal system in adolescence.[21] Similarly, Mori et al. found patients with type 1 DM have elevated risk

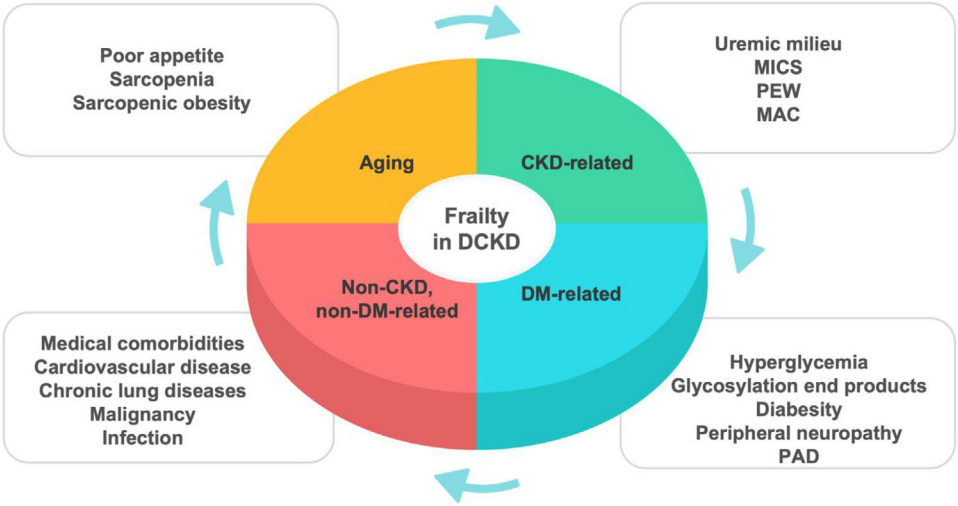

FIGURE 1 Pathogenesis of frailty in diabetic chronic kidney disease. CKD, chronic kidney disease; DM, diabetes mellitus; MAC, medial arterial calcification; MICS, malnutrition-inflammation complex syndrome; PAD, peripheral arterial disease; PEW, protein-energy wasting

for muscle weakness as a result of accumulation of advanced glycation end-prodcuts.[31]

In combination with older age, DM may synergistically reduce both physical and cognitive function,[32] creating ripe conditions for frailty and potentially increasing mortality risk.[33] Studies have shown that type 1 DM can significantly impact brain structure and function, described as type 1 DM-associated cognitive decline.[34] Tonoli et al. found that cognitive decline is more severe in adults when compared with children; suggesting that age and DM duration both contribute to reduced functional outcome, and theoretically risk for frailty.[35] Also, Chaytor et al. found the severity of overall cognitive decline was uniquely associated with measures of DM-specific self-management skills and activities of daily living.[36] Physical and neurocognitive decline particularly in adults, can lead to frailty and long-term complications. Based on risk factors associated with DM and kidney failure alone, PTx candidates appear more likely to present with frailty, when compared with kidney transplant alone candidates without DM although more investigation is needed to better characterize the effect.

2.1 | Modeling frailty mechanisms in pancreas transplant candidates

The mechanisms of frailty in diabetic CKD can be categorized as follows: aging, CKD-related, DM-related, and non-CKD-, non-DM-related factors (Figure 1). The most accepted frailty models for surgical patients invoke a series of phenotypic characteristics and cumulative deficits.[37] Based on our review, we identified four main factors that appear contributory to frailty among PTx candidates. These are: (1) underlying DM and chronic kidney disease, (2) aging, (3) environmental factors, and (4) immunological factors (Figure 2). These can impact adaption to the environment as well as social disabilities, depression and premature aging, and accelerate the frailty process.[38] While these interactions have been mostly studied and reported in older individuals, younger PTx candidates can also express the reduced physiological reserve that characterizes the frail individual. Patients with DM tend to show an accelerated aging process and associated risk of frailty[39]; among the multiple mechanisms studied to explain this phenomenon, the immune system plays a noteworthy role.[40]

2.2 | Molecular mechanisms of diabetes-related frailty

Meta-inflammation is the term used to refer to the chronic low-grade inflammatory state associated with metabolic disorders.[41,42] In patients with DM, meta-inflammation can manifest as an abnormal response to the metabolic stress generated by the nutrient surplus.[41] When compared to the beneficial inflammatory response to acute stressors, the chronic sustained activation of inflammatory stimuli of DM is considered detrimental, leading to degenerative morbidity and subsequent frailty.[27,43] The prolonged inflammatory state in DM is classically described in obese patients, where insulin resistance plays a bidirectional role in triggering inflammation during glucose overload, while also causing inflammatory β cell damage and interruptions in insulin-signal transduction.[44] Obese patients with DM also have increased circulating levels of inflammatory markers including interleukin (IL)-6, IL-8, and tumor necrosis factor-α, further driving deleterious inflammation, and contributing to frailty.[45,46]

2.3 | Diabesity

When type 2 diabetes develops with aging and is associated with obesity, the phenomenon has been described as diabesity.[47] Importantly, obesity itself is known to limit glucose tolerance and hasten development of type 2 diabetes, and conversely, even mild to moderate

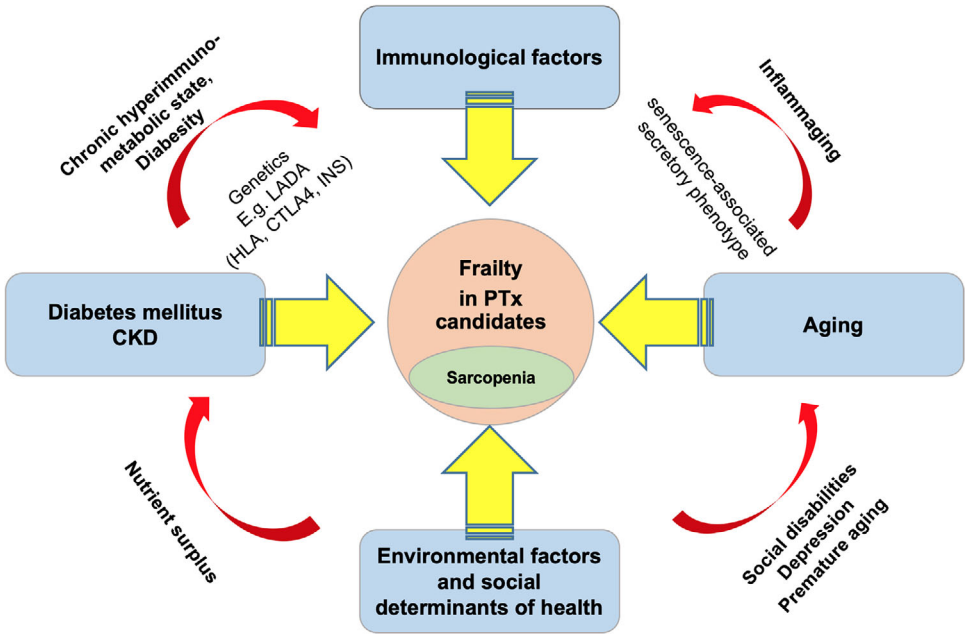

FIGURE 2 Contributing factors of frailty in PTx candidates involving in four main factors including underlying diabetes and chronic kidney disease, aging, environment, and immunological factors. CKD, chronic kidney disease; CTLA4, Cytotoxic T-Lymphocyte Antigen gene; HLA, Human Leukocyte Antigen gene; INS, insulin gene; LDAD, latent autoimmune diabetes in adults

amounts of weight loss can improve glucose sensitivity and prevent development of diabetes. Moreover, patients with peripheral neuropathy younger than 65 years of age and diabesity were found to be seven times more likely to be frail than control patients with obesity who did not have diabetes, suggesting neuropathy contributes to the early onset of frailty in patients with diabesity.[48] Transplant providers routinely consider obesity in candidate selection for PTx based on the consequences of diabesity and the evidence of increased risk for poor outcome,[49] however, well selected patients with increased body mass index (BMI) with type 1 or type 2 diabetes have demonstrated equivalent results.[50]

2.4 | Inflammaging

Age-related inflammation, so-called inflammaging, is a chronic, sterile, low-grade inflammation in older patients. Inflammaging is a known risk factor and predictor of frailty[51] leading to poor outcomes among the older recipients with major age-related diseases such as cardiovascular disease and cancers, particularly in the context of surgery.[52,53] Inflammaging may have deleterious additive effects in patients with DM who have underlying chronic inflammation.[51] Mechanisms of inflammaging are under investigation. The early development of the senescence-associated secretory phenotype by the endothelial cells, regulated by NF-kB and IL-1/NLRP3 inflammasome pathways, represents a key event in the progression into an accelerated aging rate.[51,54,55] Consequently, these pathways have been investigated as potential therapeutic targets to attenuate the accelerated senescence process, increasing the risk for frailty.[56] Given that PTx patients are aging, and have long standing DM history, both meta-inflammation and inflammaging can co-exist in the PTx candidate, potentially initiating frailty prior to transplantation.[57]

2.5 | Sarcopenia

Sarcopenia is the loss of muscle mass, and a contributor to the frailty phenotype.[58,59] The loss or malfunction of muscle cells in these patients is associated with the development of some of the classic clinical features of frailty, such as slow gait speed, decreased grip strength, poor endurance, or limited activity levels.[60] Patients with DM tend to have an accelerated aging process and are more prone to sarcopenia.[61] Several molecular mechanisms involved in inflammation, including cellular senescence, mitochondrial dysfunction, defective autophagy and mitophagy, activation of the inflammasome, dysregulation of the ubiquitin-proteosome system, activation of the DNA damage response, and dysbiosis have also been implicated in the development of sarcopenia.[62] Patients with sarcopenia have impaired cellular adaption to stress and regeneration also contributes to a catabolic process with significant clinical consequences. For instance, Mori et al. reported in a Japanese study of 36 patients with DM that the prevalence of sarcopenia and muscle weakness was 16.6% and 47.2%, respectively.[31]

2.6 | Endothelial dysfunction

Endothelial dysfunction is characterized by reduction in vasodilatation, is prothrombotic, and mimics and is associated with coronary artery disease.[63] Not surprisingly, endothelial dysfunction is more common in

patients with DM, and may contribute to frailty.[63,64] There are minimal data regarding endothelial function after PTx. However, experimental studies have demonstrated a reversal of documented pre-PTx endothelial dysfunction.[65] Mechanistically, after PTx, an increase in NO_2^- due to improved blood sugar control has been associated with an increase in flow-mediated dilatation response, used as a surrogate for improved endothelial function.[65] The combination of improved metabolic control with the reversal of endothelial dysfunction is likely responsible for the improved cardiovascular outcomes seen in SPK recipients, and may further contribute to improve functional capacity and reduction in frailty after transplantation.[64,66] This effect is suggested by the findings of a more pronounced reversal of endothelial dysfunction noted on SPK patients compared to kidney-only transplant patients over a follow-up of 58 ± 31 months, despite the fact that inflammatory marker levels did not differ between groups.[65]

2.7 | Immune dysfunction

From the immunological perspective, an interesting subgroup of patients in whom to study frailty are those with latent autoimmune diabetes in adults (LADA). LADA accounts for about 10% of the total patients with DM and this subpopulation may be underdiagnosed and overrepresented among the PTx candidates given their particular clinical characteristics.[67] Patients with LADA often have onset of DM at 30 years or older, non-obese, with the initial control of glycemia on oral agents that, over months, progress to an insulin requirement in the setting of low fasting C-peptide and positive anti-glutamic acid decarboxylase (GAD) antibodies.[68]

Genes encoding for Human Leukocyte Antigen, Cytotoxic T-Lymphocyte Antigen, and insulin have been associated with the pathogenesis of LADA.[69,70] However, the studies were limited to previously identified genes associated with type 1 DM (such as GAD and intracytoplasmic IA-2), leaving unanswered a potential unique genetic susceptibility pattern. [71,72] From a PTx candidacy perspective it is not known if a propensity exists for LADA patients to develop frailty differently versus patients with type 1 or type 2 DM.[73]

3 | INSTRUMENTS FOR IDENTIFYING FRAILTY IN PANCREAS TRANSPLANT CANDIDATES

There is a strong evidence associating frailty with poor surgical and post-transplantation outcomes.[74,75] Frailty assessment instruments are increasingly being used in the clinical decision making process to risk-stratify transplant candidates,[74] identify the potential for reversibility, as well as improve outcomes with the incorporation of interventions.[76] Currently, there are over 75 frailty screening tools available for use that primarily focus on physical or phenotypical frailty assessment.[76] Several of these tools have been assessed in the solid organ transplant population with most data coming from the kidney transplant population. The 2018 report of the AST consensus conference provided best practices for frailty risk assessment in solid organ transplantation, however, no specific guidelines were provided for assessment in the PTx recipients.[3]

Patients with type 1 DM typically present at less than 50 years of age and are phenotypically different from those type 2 DM who are frequently older than 50 with more obesity and other comorbid conditions.[25] Furthermore, end organ damage resulting from complications from DM (such as retinopathy, peripheral arterial disease, complications associated chronic kidney disease, limited strength in the arm with dialysis vascular access) often make it challenging to administer physical performance tools in this complex population. Therefore, there is greater need to identify optimal frailty screening methods for this population especially given the lack of clear performance advantage of any one of the tests (Table 1).

3.1 | Test selection: Background

When selecting a test, transplant physicians must take into consideration not only the candidates' ability to perform the task but also the ease of test administration, inter-user reliability, and reproducibility.[77] Since most PTx occur as part of an SPK, we can extrapolate assessment methods applied to the kidney transplant population for use in PTx candidates.

While the Fried Frailty Phenotype (FFP) is the most extensively validated frailty tool, in a recent survey by McAdams-DeMarco et al., amongst kidney transplant centers, 19 different frailty assessment tools were reported as being used amongst 133 kidney transplant programs in the United States.[78] Objective measures of physical performance such as walking speed, grip strength, repeat chair stands, and 6-min walk test were primary assessment techniques utilized across transplant centers (Table 1). Despite this, Karnofsky Performance Score remains the only frailty measurement method required to be reported by the Organ Procurement and Transplantation Network.[79] However, being a completely subjective assessment method, there are significant concerns about the inter-rater variability and reliability of such a subjective proxy.[79]

3.2 | Test selection: Our recommendation

Young patients with DM may develop significant frailty. Therefore, special consideration is needed when selecting an assessment tool that will reliably assess for frailty, regardless of age, thereby minimizing the subjective provider perception of older adults being frail.[80] Overall, instruments to assess frailty specifically tailored to PTx candidates are currently lacking, although there are tools that at least partially apply to patients with DM and its comorbidities. Given these limitations and the complexities of PTx candidates, a multidimensional testing strategy is almost certainly a necessity. We recommend utilizing the two assessment methods: Fried Frailty Phenotype (FFP) and short physical performance battery (SPPB).

We believe this combination of tests combines the most validated tool, FFP, with another well validated, but more objective assessment,

TABLE 1 Functional tools reported to be used by transplant centers

Functional assessment tools	Utilized by transplant centers	Methods	Benefits	Limitations
Karnofsky Performance Status Scale (KPS)		Assigned score 0%–100% based on reported functional abilities.	Easy to administer Quickly identifies sickest group	Subjective Variability in reporting
Fried's Frailty Phenotype Score (FFP)	8%	Score 0–5 on domains, namely: 1. weight loss 2. exhaustion 3. physical activity 4. grip strength 5. walking speed Scoring interpretation:0: non-frail1–2: pre-frail≥3: frail	Widely used in research Well validated	Has subjective and objective components, Time consuming, In clinical practice not accurately performed leading to errors
Physical Performance Capacity Measures	11%–19%	walking speed, grip strength, repeat chair stands, 6-min walk test, timed up and go tests	Easy to administerLow/no cost Not time consuming	Assesses specific functions and muscle groups, Not great stand-alone tests
SPPB	5%	Measures lower extremity strength and balance.Score from 0 to 4 on: 1. standing balance, 2. walking speed, 3. chair sit-to-stand tests Score<10: SPPB impaired.	Completely objective Well validated in older, CKD and transplant populations, Easy to administer, Not time consuming	Assesses lower extremity only and cannot be used in those with lower extremity amputations or impairments.
Morphometric Measurements	8%	1. *Sarcopenia diagnosed by muscle mass measured by*: Anthropometry, Bioelectrical Impedance Analysis (BIA), Dual Energy X-ray Absorptiometry (DEXA scan), CT or MRI imaging 2. *Morphometric Age Calculation*: using psoas muscle area, psoas muscle density and percentage of aortic wall calcification measured on abdominal CT imaging	Objective, No additional studies necessary for transplant population as imaging studies done frequently Objective, No additional studies necessary for transplant population as imaging studies done frequently	Expensive, Requires trained personnel, No clear diagnosing criteria leads to under diagnosis. Expensive, Requires trained personnel, Needs special software

Abbreviations: CKD, chronic kidney disease; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; IADL, instrumental activities of daily living; PASE, physical activity scale of the elderly; SPPB, performance-based functional assessment; SF-36, short form 36.

SPPB, to successfully identify most PTx candidates with frailty.[81] SPPB is simple and efficient to perform in populations with similar characteristics to PTx candidates, such as older, CKD, and transplant populations. Limits to our approach exist. This testing approach may require workflow adjustments and new documentation for staff at certain programs. Amongst patients who are physically unable to perform tests of speed and strength, morphometric measurements assessing for sarcopenia can be used as an adjunct frailty assessment.[82] In this scenario, given lack of evidence we would not recommend modifying the scores of FFP and SPPB testing as this would be arbitrary. Instead, we suggest utilizing morphometric testing for sarcopenia assessment within FFP, such as psoas muscle thickness within cross-sectional imaging, as has been previously reported.[82]

Undoubtedly, until more data and experience with these tests is acquired in PTx candidates, clinical judgement will remain critical for selection. Overall, although large prospective studies are needed, we consider FFP and SPPB the best combination of tests to identify frailty in PTx candidates.

4 | PANCREAS TRANSPLANT WAITLIST OUTCOMES AND SURROGATES OF FRAILTY

Ages of patients for patients listed for PTx has changed in the past decade. From 2008 to 2020 the number of PTx waitlist patients aged 35–44 declined from 40% to 35% while patients 55 and older increased from 7.5% to over 10%.[16] The number of new patients on the SPK waitlist increased in 2019 (driven mostly by SPK listings and patients with type 2 DM) as it had since the pancreas allocation change in 2014, while total adult listings for PTA and PAK continued to trend down.[18]

TABLE 2 Main outcomes of PTx waitlist candidates in 2020[a]

Outcomes	Data[16,18]
PTx	PTx rate in transplants/100 waitlist-years • Overall, 40.2 (44.7) • Median time to transplant in SPKs 14.1 months in 2019–2020 and 12.3 months in 2017–2018 By types of DM in transplants/100 waitlist-years • Type 1 DM: 38 (42) • Type 2 DM: 50 (60.6) By PTx candidate types in percentage: • SPK: 77.0% • PAK: 10.2% • PTA: 12.8%
LDKT	3.7% of SPK candidates who may also be later listed for PAK (4.3%)
Death	6.1 deaths/100 waitlist-years (4.6%) Waitlist mortality by types of PTx/100 waitlist-years • SPK: 6.9 (5.6) • PAK: 3.2 (.9) • PTA: 4.2 (2.7)
Death after removal from the waiting list	8.5% (5.3%) of patients died within 6 months after waitlist removal for reasons other than PTx Waitlist death rate by types of PTx • SPK: 8.2% (6.0%) • PAK: 7.2% (2.7%) • PTA: 8.3% (4.2%)

Abbreviations: DM, diabetes mellitus; LDKT, living donor kidney transplantation; PAK, pancreas after kidney transplant; PTx, pancreas transplantation; PTA, pancreas transplant alone; SPK, simultaneous pancreas and kidney transplant.

[a]Numbers in paratheses are from 2019.

The COVID-19 pandemic profoundly impacted pancreas transplantation in 2020,including as the number of listings of patients over the age of 55 drifted to 10.1% from 10.7% in 2019.[16] Pre-transplant pancreas candidate mortality has decreased from 2008 until 2019, while waitlist mortality in all age groups has remained relatively stable over the past 4 years and rates were not consistently different by sex or race (Table 2).[18]

Using functional status as a surrogate marker of frailty, centers that reported Karnofsky Performance Score (KPS) was positively associated with a graded survival in the waitlist PTx candidates. From a retrospective cohort study using Scientific Registry of Transplant Recipients data and dividing PTx candidates into four groups based on KPS at the time of listing (normal functional status (80–100), capable of self-care (70), requires assistance (50–60), and disabled (10–40)), an estimated 5-year survival on the waiting list was 77.5%, 74.7%, 76%, and 65.9%, respectively.[6] Although the poorest functional status at the time of PTx listing is associated with greater waitlist mortality, additional studies are required to evaluate the effect of improving functional status on survival, which may guide waitlist management in this population.

Strategies to shorten PTx waiting time are important as frailty and morbidity from DM and CKD on the waitlist may compound over time. A single-center retrospective observational study reported an average 483 day decrease in PTx waitlist times by performing PTx from imported organs compared to the median national waitlist time reported by the United Network for Organ Sharing (UNOS) in Region 9, which has a PTx waiting time longer than average (1001 vs. 518 days). Although patients who received an imported pancreas had a greater length of stay and transplant cost compared to those receiving PTx from the local pool, postoperative complications, and 1-year hemoglobin A1c (HbA1c) were not different.[83]

Obesity in advanced CKD and ESKD has a protective effect on mortality outcomes; likewise in the geriatric population.[84,85] However, those with older age and obesity have higher risk for frailty.[86,87] The underlying mechanism may be related to increased inflammation,[77,88] low antioxidant, [89] and possibly sarcopenic obesity characterized by mismatch of fat mass to muscle mass.[90,91] Although there is an association of pathogenesis between obesity and sarcopenia with poor post-transplant outcomes, evidence of the association between obesity, frailty and mortality in waitlisted PTx candidates is lacking.[92] Further studies of traditional risk factors related to frailty may improve outcomes in waitlist PTx candidates.

Unlike in the kidney transplantation literature, the impact of frailty on patient selection for waitlist PTx candidates has not been well investigated. Haugen and colleagues studied 7078 candidates across three different centers in a prospective fashion and demonstrated that frailty is associated with a lower chance of waitlisting and a lower rate of kidney transplantation.[93] Programs who study frailty in PTx candidates need to balance the benefits of PTx against the risks of frailty and reduced access to PTx, as even patients with significantly reduced functional status have been shown to have mortality benefit and frailty is a potentially modifiable risk factor (see Section 5).[6]

On the PTx waitlist malnutrition has the potential to increase the risk of frailty. Malnutrition is often a consequence of the underlying inflammation that is common among patients with advanced age, obesity, DM, and CKD/ESKD.[94–96] Patients with diabetes mellitus can have significant malnutrition related to a variety of gastrointestinal dysmotility disorders, such as gastroparesis, most commonly, but also slow intestinal transit, delayed colonic emptying, and constipation.[97–99] These secondary complications of diabetes result from loss of interstitial cells of Cajal and neural abnormalities, which potentiate risk for malnutrition, diminished musculoskeletal reserve, and frailty.[100–103]

A subjective global assessment based on features of the history and physical examination is considered a reliable bedside tool for diagnose of malnutrition and can identify those who would benefit from nutrition care, while also predicting outcomes.[104] A study using subjective global assessment in wait-listed SPK candidates showed that patients may have evidence of malnutrition despite normal body mass index (BMI).[105] Further studies related to nutrition and specific phenotypes of malnutrition either undernutrition and overnutrition such as sarcopenic obesity may provide additional explanation related to outcomes with frailty risk and may predict outcomes after PTx.

5 | FRAILTY IN PANCREAS TRANSPLANT RECIPIENT OUTCOMES

We found increased age, a risk factor for frailty, and its influence on PTx outcomes has drawn the attention of investigators. Our growing aging population has led to more patients with DM reaching older age in better health; it has also resulted in increased numbers of patients with DM considering and receiving PTx.[11,106–112] Age is known to be the major risk factor for adverse patient outcomes following kidney transplantation.[113] Some studies demonstrated inferior outcomes among PTx recipients aged 50 years or older.[11,110,114] In 2014, Siskind et al. conducted a registry-based study using the UNOS database of 20 854 patients (3160 patients aged 50–59 and 280 patients aged ≥60 at the time of PTx).[110] The investigators demonstrated a significant correlation between increasing recipient age and decreased patient and graft survivals, especially in the recipients aged 60 years or older.[110] However, more recent studies suggest comparable patient and graft survivals after PTx among older (aged ≥50 years) and younger patients with careful medical assessment and patient selection (Table 3).[11,106,107,109–112] For example, Ablorsu et al. found the one-year complication rate and patient survival is similar for pancreas recipients ≥50 versus <50 years of age[112] In centers experienced in PTx, nearly similar results can be achieved in older recipients.[108,109] Although factors contributing to better outcomes were not identified, these may include an improvement in surgical techniques, immunosuppression therapy, and post-PTx care.[108] Thus, concern for frailty, extrapolated through advanced age alone, should no longer be considered a contraindication to PTx.[106,107,109,112]

Increased age (only one of the risks for frailty) does not independently affect outcomes after PTx.[11,106,107,109–112] As stated above, we know that recipient functional status and sarcopenia (surrogates for frailty) inform outcomes after surgery and after PTx (Table 4).[6,115–118] From the aforementioned study, the association between KPS and post-PTx survival was examined.[6] Among the SPK recipients, 58% had normal functional status, 25% were capable of self-care, 14% required assistance, and 3% were disabled. There was also a graded increase in mortality after transplant with impaired functional levels, independent of age.[6] Nevertheless, after the peri-operative period, SPK recipients across all functional status levels had a decreased 5-year mortality compared with continued waiting (70% reduction in those with normal functioning and 52% risk reduction among disabled patients).[6] Thus, the life-saving capacity of SPK is still apparent in well selected patients even when a surrogate marker of frailty is present.

Recently, there has been increasing interest and with conflicting results in the prediction of outcomes after PTx when examining sarcopenia through such proxy measurements as psoas muscle mass index (PMI) and psoas muscle area.[115–118] Several studies demonstrated significant associations between low psoas muscle readings and increased resource utilization[116] and pancreas allograft failure.[115] However, a recent study demonstrated no significant impact of low PMI on outcomes after PTx, including postoperative complications or 5-year patient survival.[118]

Given the conflicting data regarding potential risk factors of sarcopenia, and poor functional status on the outcomes after PTx, the underlying mechanism of the frailty syndrome needs to be further elucidated. Additional immunologic factors after PTx can play a role; therefore, definitions and suitable diagnostic criteria may need to be justified.

Quality of life has been shown to improve following pancreas transplantation to a greater extent than in kidney transplant alone, however, the impact of frailty on this effect has not been described.[119] Compared to patients who underwent kidney transplant alone, SPK recipients reported better values on a Kidney Disease and Quality of Life Short Form[120,121] Patients with type 1 diabetes who underwent SPK have reported improved quality of life on specific metrics around kidney disease and diabetes compared with those on the waitlist for SPK.[122]

6 | INTERVENTIONS TO MITIGATE FRAILTY PRE- AND POST-PANCREAS TRANSPLANTATION

Diabetes mellitus can portend frailty, sarcopenia, and diminished functional status; ultimately impacting surgical outcomes, and long-term survival.[57,123] In potential kidney transplant patients, it is clear that the level of frailty can be altered over time; however, DM has been associated with resilient frailty between the time evaluation and transplantation, suggesting DM could be a durable indicator of unfavorable frailty transitions.[124] Nevertheless, following a successful PTx engraftment, reduced or reversal of macrovascular and microvascular damage can be seen,[125] suggesting a mechanism for frailty improvement after PTx. Given the potential to stabilize or improve frailty, as well as sarcopenia and muscle strength, active interventions such as exercise programs are recommended for PTx candidates and recipients.[126]

6.1 | Exercise interventions

The value of strength testing and exercise programs has been known for over a century.[127] In the modern era, supervised exercise programs have been used for patients with peripheral arterial disease for three decades, originally for the mitigation of disease symptoms such as claudication, and more recently for pre-habilitation purposes (see below). However, their availability and utilization are often logistically problematic.[128,129] Interventions for those with CKD have been summarized by the AST KPCOP Frailty Workgroup recently.[30] Monitored walking programs for dialysis patients have shown limited success, and continuation after program cessation is challenging.[130] Both resistance and aerobic intradialytic exercise has shown some promise as well.[131,132] Typically, as in intervention studies in other fields,[133] these exercise interventions do not directly measure effects on frailty per se, but often measure outcomes in the context of the related concepts of sarcopenia, functionality, or other surrogate endpoints. For example, a recent study of obese older adults found that weight

TABLE 3 Age and pancreas transplant outcomes

Reference, Year	Design and participants	Age distributions	Associations of age with posttransplant outcomes	Other key findings
Ablorsu et al, 2008[112]	• Retrospective single center cohort (06/2001–12/2007) • *N* = 135 PTx recipients (109 SPKT, 22 PAK, and four PTA).	• <50 years: 77% • ≥ 50 years: 23%	1-year patient survival • <50 versus ≥50 years: 92% versus 88% ($p = .40$) Pancreas graft survival • <50 versus ≥50 years: 74% versus 79% ($p = .40$)	• No significant difference in urinary tract infections and early rejection by age. • Respiratory tract infection was significantly higher in age > 50 versus <50: 38.7% versus 9.6% ($p = .003$).
Schenker et al, 2011[106]	• Retrospective single center cohort (06/1994–06/2009) • *N* = 398 PTx recipients	• <50: 83% • ≥ 50 years: 17%	*Outcomes at 1, 5, and 10 years* Patient survival • <50 years: 97%, 89%, 84% ($p > .05$) • ≥50 years: 100%, 89%, 80% Kidney graft survival • <50 years: 97%, 91%, 69% ($p > .05$) • ≥50 years: 95%, 81%, 74% Pancreas graft survival • <50 years: 83%, 72%, and 67% ($p > .05$) • ≥50 years: 87%, 76%, and 67%.	• No significant differences in acute rejection or surgical complications (e.g., relaparotomy, pancreas graft thrombosis) by age.
Shah et al, 2013[111]	• Retrospective single center cohort (01/2003–12/2011) • *N* = 405 PTx recipients (216 SPK, 93 PAK, 96 PTA)	• <30 years: 9% • 30–39 years: 27% • 40–49 years: 39% • 50–59 years: 21% • ≥60 years: 4%	1-year graft and patient survival • Similar across age groups. 5 year graft survival • <30 years: 74%, versus ~ 80% for other ages (p = NS).	5-year patient survival • <30 years: 92% versus 84% for ≥50 years (p = NS).
Siskind et al, 2014[110]	• Registry based: UNOS/SRTR registry (1996–2012) • *N* = 20 854 PTx recipients	• 18–29 years: 9% • 30–39 years: 37% • 40–49 years: 38% • 50–59 years: 15% • ≥60 years: 1%	Patient and graft survival • Lower in PTx recipients >60 vs <50 year ($p < .001$) *Outcomes at 5, 10, and 15* years Patient survival • 18–29 years: 86%, 74%, 65% • 30–39 years: 88%, 77%, 66% • 40–49 years: 86%, 72%, 56% • 50–59 years: 82%, 62%, 42% • ≥60 years: 71%, 43%, 0% Graft survival • 18–29 years: 57%, 40%, 27% • 30–39 years: 66%, 48%, 33% • 40–49 years: 68%, 52%, 37% • 50–59 years: 67%, 48%, 29% • ≥60 years: 60%, 30%, 0%	1- and 3-year graft survival • 18–29 years: 81%, 67% • 30–39 years: 83%, 73% • 40–49 years: 83%, 75% • 50–59 years: 84%, 75% • ≥60vs: 82%, 70%

(Continues)

TABLE 3 (Continued)

Reference, Year	Design and participants	Age distributions	Associations of age with posttransplant outcomes	Other key findings
Gruessner et al, 2016[11]	• Registry based: UNOS and International Pancreas Transplant Registry (IPTR) registries in two periods, 2005-2009 and 2010-2014 • *N* = 11 940 PTx recipients	SPKT (2005–2009) • <30 years: 7% • 30–44 years: 55% • 45–59 years: 36% • ≥60 years: 1% SPKT (2010–2014) • <30: years 8% • 30–44 years: 53% • 45–59 years: 38% • ≥60 years: 1% PAK (2005–2009) • <30 years: 6% • 30–44 years: 53% • 45–59 years: 39% • ≥60 years: 2% PAK (2010–2014) • <30 years: 6% • 30–44 years: 48% • 45–59 years: 43% • ≥60 years: 3% PTA (2005–2009) • <30 years: 15% • 30–44 years: 46% • 45–59 years: 36% • ≥60 years: 3% PTA (2010–2014) • <30 years: 11% • 30–44 years: 41% • 45–59 years: 43% • ≥60 years: 6%	*Reference 30–44 years* **SPK** Patients >45 years had 58% higher risk of death. Patients aged 15–29 years had higher risk of pancreas (RR 1.26) and kidney graft failure (RR 1.86) **PAK** No association of age with patient and pancreas graft survival **PTA** Patients >45 years had 197% higher risk of death. Patient aged15–29 years had higher risk of pancreas graft failure (RR 1.56)	• Trend towards higher proportion recipients age >50 years in 2010–2014 versus 20052009: • Among PTA: 32% versus 22% • Among PAK: 28% versus 22% • Among SPKT: 22% versus 20%.
Scalea et al, v2016 [109]	• Retrospective single center cohort (07/1999—06/2012) • *N* = 740 PTx recipients	• 25–34 years: 17% • 35–44 years: 32% • 45–54 years: 23% • ≥50 years: 3%	Patient survival • Comparable for younger and older PTx recipients. Death-censored and all-cause pancreas graft survival • Similar in younger and in older patients.	• The incidence of pre-transplant evaluation cardiac catheterization increased incrementally across age, suggesting variation in pre-PTx evaluation

(Continues)

TABLE 3 (Continued)

Reference, Year	Design and participants	Age distributions	Associations of age with posttransplant outcomes	Other key findings
Mittal et al, 2020 [107]	• Retrospective single center cohort (2002–2016) • $N = 527$ PTx recipients	• 23–54 years: 84% • 55–67 years: 16%	Mortality • increased with older recipient age: HR 1.63 per 10-years older age Death-censored pancreas and kidney graft survival • No differences across age groups.	• ~40% of recipients who died in the first-year post-transplant had early graft loss.
Montagud-Marrahi et al, 2020 [108]	• Retrospective single center cohort (2000–2016) • $N = 338$ PTx recipients	• <50 years: 88% • ≥50 years: 12%	Death-censored pancreas graft survival at 1, 5 and 10 years • <50 years: 89%, 82%, and 76% • ≥50 years: 90%, 90%, and 90% ($p = .24$)	• Diabetes vintage (HR 1.05, $p = .03$) and pre-PTx MACE (HR 1.98, $p = .011$), but not recipient age (HR 1.45, $p = .339$), were associated with post-transplant MACE.

*$p < .05$.

Abbreviations: HR, hazard ratio; IMAC, intramuscular adipose tissue content; KPS, Karnofsky Performance Score; MACE, major adverse cardiac events; SPKT, simultaneous pancreas-kvidney transplant; PF, physical function; PMI, Psoas muscle mass index; PAK, pancreas after kidney transplant; PTx, pancreas transplant; PTA, pancreas transplant alone; SR, self-report; SRTR, Scientific Registry of Transplant Recipients; UNOS, United Network for Organ Sharing.

loss, combined with aerobic and resistance exercise, could improve their functional status as measured by peak oxygen consumption and strength, although both types of exercise also showed benefit in isolation from the other.[134]

Many of these studies, particularly those for CKD, have included a significant population of patients with DM. There are also several studies and meta-analyses on the effects of exercise interventions in patients with DM. Notably, aerobic exercise-based studies are more common than resistance exercise, at least in the context of type 2 DM.[135] Many of the studies in type 1 DM focus on the effects of exercise programs on younger patients, possibly before the meaningful onset of frailty. However, some early surrogate outcomes are relevant. Exercise-induced reduction in HbA1c, BMI, low-density lipoprotein, and waist circumference have been variably reported, and the results are inconsistent across studies.[136–140] Given that the younger type 1 DM population is overrepresented in PTx candidates, it is reasonable to conclude that such interventions may have beneficial cardiovascular effects over time, thereby potentially impacting performance status and potentially frailty, consistent with effects seen with interventions that have been shown for those with type 2 DM.[141,142]

6.2 | Pre-habilitation

While data on frailty interventions for PTx surgery specifically is relatively sparse, there is better data for interventions for those with DM and ESKD, as well as for exercise-based programs timed for a specific operation and designed to improve surgical outcomes—termed pre-habilitation. Often, these interventions involve a multimodal approach, including structured or unstructured exercise programs, smoking cessation, lifestyle changes, and nutritional guidance. Intervention for frailty in PTx candidates and recipients are summarized in Table 5.

Pre-habilitation consists of exercise, nutritional, and lifestyle interventions timed to improve surgical outcomes. Pre-habilitation has been shown to have positive physiological effects and reduce length of stay and costs, although it is unclear how compliant patients remain once formal program participation ends and how long improvements last after that time.[142–146] Also, although it is unclear if pre-habilitation can directly reduce frailty, it clearly has benefits.

Cardiovascular disease is common both pre-and post-transplant and strongly linked with frailty.[147–149] Although literature specific to PTx is missing, cardiac rehabilitation has been shown to increase the level of physical activity[150] and reduce cardiovascular mortality[151] in the general population. Pulmonary rehabilitation is frequently utilized as a conditioning program before and after lung transplant and in lung conditions like asthma, chronic obstructive lung disease, bronchiectasis, and pulmonary hypertension to improve exercise capacity, and overall quality of life.[152–156] Pancreas transplant candidates with associated lung disorders may similarly benefit from pulmonary rehabilitation.

As most PTx necessitates a suitable deceased donor, akin to deceased donor kidney transplantation, it is almost always an unscheduled and potentially difficult to time pre-habilitation.[157] However, in a pilot study of 18 kidney transplant candidates receiving weekly

TABLE 4 Frailty measures: Functional status, sarcopenia and pancreas transplant outcomes

Reference, Year	Design and participants	Frailty, functional status, sarcopenia measure	Frailty distributions	Associations of frailty with posttransplant outcomes	Other key findings
Parsons et al, 2018 [116]	• Retrospective single center cohort • *N* = 100 pancreas transplant (SPKT and PAK) recipients	• KPS at the time of transplant • Psoas muscle area	• Mean KPS: 76.5 ± 9.6	• Sarcopenia on peri-transplant cross-sectional imaging correlated with burden of readmissions ($p = .007$)	• Sarcopenia predicts resource utilization in the first year after transplant better than comorbidities or standard measures such as performance status.
Noguchi et al, v2018 [117]	• Retrospective single center cohort (08/2001–05/2016) • *N* = 43 (32 SPKT and 11 PTA/PAK)	• Psoas muscle mass index (PMI), preoperative	• Mean PMI: 6.66 ± 2.12 cm2/m2 • Low PMI: 27.9% • Normal PMI: 72.1%	*Outcomes (Low PMI versus Normal PMI)* All cause graft loss • 0/12 (0%) versus 12/31 (38.7%) Patient Survival • 92% versus 100% Acute rejection • 36% versus 48%	• Low PMI was not associated with acute rejection.
Fukuda et al, 2018 [118]	• Retrospective single center cohort (04/2000-03/2017) • *N* = 41 (36 SPKT, four PAK, and one PTA)	• PMI and intramuscular adipose tissue content (IMAC), preoperative	• Low PMI: 26.8% • Normal PMI: 73.2% • Normal IMAC: 73.2% • High IMAC: 26.8% • Sarcopenia • (based on PMI and IMAC stratifications): 26.8%	Postoperative complications • High IMAC versus normal IMAC: 72.7% versus 23.3% ($p = .008$) • Low PMI versus normal PMI: 45.5% versus 33.3% ($p = .49$) 5-year survival • High IMAC versus normal IMAC: 55% versus 85% ($p = .04$) • Low PMI and normal PMI: 73% versus 78% ($p = .30$)	• Low PMI was not associated with postoperative outcomes.
Lentine et al, 2020 [6]	• Registry based: UNOS/SRTR registry between 2006 and 2019 • *N* = 16 822 SPKT candidates and 10 316 SPKT recipients	• KPS at the time of listing (for candidate) and at transplant (for recipients)	Candidates • KPS 80–100: 62.0% • KPS 70: 23.5% • KPS 50–60: 12.4% • KPS 10–40: 2.1% Recipients • KPS 80–100: 57.8% • KPS 70: 24.7% • KPS 50–60: 14.2% • KPS 10–40: 3.3%	*Reference: KPS 80–100* Death • KPS 70: aHR 1.18 • KPS 50–60: aHR 1.3* • KPS 10-40: aHR 1.55* • Kidney graft loss • KPS 70: aHR 1.03 • KPS 50–60: aHR 1.18* • KPS 10-40: aHR 1.23 Pancreas graft loss • KPS 70: aHR 1.02 • KPS 50–60: aHR 1.10 • KPS 10-40: aHR .85	• Compared with waiting, SPKT was associated with 2-fold mortality • risk within 30 days of transplant. • Beyond 30 days, SPKT was associated with reduced mortality, from 52% for disabled patients (aHR, .48) to 70% for patients with normal functioning (aHR, .40).
Meier et al, 2020 [115]	• Retrospective single center cohort (2010- 2018) • *N* = 107 SPKT recipients	• PMI, perioperative	• Low PMI: 21.5% • Normal PMI: 78.5%	Pancreas graft failure • Low PMI independently associated (HR 5.4, $p < .05$) Patient and kidney graft survival • Not statistically different between groups ($p = .85$ and $p = .36$, respectively)	• Among low PMI patients who had a follow up CT scan, 62.5% (5/8) of those with a functional pancreas graft either improved or resolved sarcopenia.

*$p < .05$

Abbreviations: HR, hazard ratio; IMAC, intramuscular adipose tissue content; KPS, Karnofsky Performance Score; PF, physical function; PMI, Psoas muscle mass index; PAK, pancreas after kidney transplant; PT, pancreas transplant; PTA, pancreas transplant alone; SPKT, simultaneous pancreas-kidney transplant; SR, self-report; SRTR, Scientific Registry of Transplant Recipients; UNOS, United Network for Organ Sharing

TABLE 5 Summarized intervention for frailty in waitlist PTx candidates and recipients

Intervention	Components	Examples	Limitations
1. Exercise			
1.1 Pretransplant	Supervised exercise programs Strengthen exercises Aerobic exercises Resistance exercises	Monitored walking programs for dialysis patients	Low rate of continuation after program cessation
1.2 Prehabilitation	Composed of exercise, nutritional, and lifestyle interventions	positive physiological effects and reduces the length of stay and costs	Difficult to time with transplantation
1.3 Post-transplant	Lack of study in PTx recipients		Logistic difficulty
2. Nutrition	Early enteral nutrition		
	Parenteral nutrition to decrease early episodes of hyperglycemia		
3. Pharmacological	Post-transplant hyperglycemia	Dipeptidyl peptidase-4 (DPP-4) inhibitor such as sitagliptin	Prolongs the time to insulin therapy
	Osteoporosis	Supplemental calcium and vitamin D Bisphosphonate Denosumab	

physical therapy demonstrated an improvement of 64% of physical activity at 2 weeks.[20] For liver transplantation, pre-transplant participation in a comprehensive exercise training program was associated with trends toward shorter lengths of stay and 90-day readmissions.[158] Given possible benefits for other organ transplants, it is reasonable to propose that those undergoing PTx would similarly benefit.

6.3 | Post-transplant interventions

Although data specific to frailty interventions after PTx are limited, amelioration of ongoing cardiovascular damage from DM has been found after PTx which could have downstream impacts on frailty.[125] For kidney transplant recipients, frailty initially worsens, but then improves by 3 months,[159] suggesting a similar dynamic may occur for PTx patients. Given the dual correction of uremia and hyperglycemia achieved in SPK recipients, it is reasonable to assume that interventions successful in kidney transplant recipients might apply to SPK recipients (and PTx recipients), although the mechanisms and timing may be different. Post-kidney transplant structured exercise trials in the US and UK have demonstrated improved peak oxygen uptake and muscle strength.[160,161] For PTx patients, when compared to normal controls, there are some subtle differences in exercise-induced insulin and glucagon changes without differences in blood glucose levels,[162] suggesting that exercise intervention can have similar effects in PTx recipients as for the general population.

Following PTx, improvement in symptoms of gastroparesis has been described with associated electrogastrography normalization.[163] However, the management of gastroparesis (a risk factor for frailty) after PTx remains a challenge as immunosuppression remains imperative, often requiring sublingual tacrolimus.[164] A well protocolized stepwise management of gastroparesis, including early oral intake, narcotic minimization, pharmacological therapies, and possibly pylorus-directed interventions has been advocated.[165]

6.4 | Nutritional and pharmacological interventions

Early enteral nutrition—a strategy to potentially mitigate frailty after PTx—may improve the nutritional requirements and decrease the need for parenteral nutrition after SPK.[166] If parenteral nutrition is required, a mixed regimen (70% carbohydrates, 30% lipids) started 24 h post-transplantation has been shown to reduce early episodes of hyperglycemia.[167] Early treatment of hyperglycemia after PTx with using a dipeptidyl peptidase-4 (DPP-4) inhibitor such as sitagliptin prolongs the time to insulin therapy compared with a standard observation approach.[168]

Other possible risk factors for frailty include osteoporosis and fragility fractures, which represent serious complications for the PTx recipients. The recommended osteoporosis therapy for organ recipients involves supplementation with calcium and vitamin D and bisphosphonate administration. In a study evaluating 63 patients with osteoporosis following solid organ transplantation (15 patients after SPK), treatment with calcium, vitamin D supplementation, and 60 mg of denosumab every 6 months for the mean duration of $1.65 \pm .7$ years improved bone density.[169] The authors concluded that denosumab could be a viable therapeutic option for transplanted patients with osteoporosis, especially in those with renal function impairment or bisphosphonate intolerance.

7 | CONCLUSIONS AND FUTURE DIRECTIONS

Based on current literature frailty likely plays an important role in the outcomes of PTx candidates and recipients. As the population with age-related diseases increases, frailty is likely to continue to become more common in PTx candidates. The pathogenesis of frailty in this population is complex and involves the interplay between non-immunologic and immunologic factors. Objective measures of frailty exist and need broader implementation and investigation to improve our

Box 1: Take-home points and suggested areas for future research

Take-home points	Areas for future research/study
1. Although frailty-related risk factors, including poor functional status and malnutrition, both under- and over-nutrition such as sarcopenia, sarcopenic obesity, and malnutrition inflammation complex syndrome are associated with poor outcomes in PTx recipients, some factors such as age is associated with inconsistent outcomes.	• Propose a specific definition of frailty for PTx candidates and recipients • Examine outcome epidemiological studies related to geriatric syndromes by incorporating traditional cardiovascular risk factors and body composition related to nutrition to further justify the definition and diagnostic criteria in PTx recipients • Create a composite score of frailty in PTx recipients to predict post-PTx outcomes
2. Association between pre-transplant sarcopenia and poor PTx and patient outcomes is inconclusive.	• Validate screening or diagnostic tools for sarcopenia especially tests for body composition in PTx candidates and recipients • Perform correlation studies to predict post-transplant outcomes in sarcopenic PT candidates • Conduct observation studies or clinical trials to determine non-pharmacological therapy to mitigate poor outcomes of pancreas and kidney allograft functions and patient survival, for example, role of low dietary protein intake, low dietary sodium intake, plant-based diet
3. Frailty or poorer functional status at the time of PTx listing is associated with greater waitlist mortality.	• Conduct studies evaluating the effect of functional status improvement on survival in waitlist PTx candidates and on transplant outcomes in PTx recipients • Perform studies on the intervention for traditional risk factors related to frailty and outcomes in waitlist PTx candidates
4. Frailty interventions in PTx recipients are lacking.	• Perform clinical trials to examine the effect of post-transplant exercise programs on transplant outcomes
5. Intervention to improve frailty in diabetic CKD and PTx candidates includes multimodal and multidisciplinary approaches. The interventions may benefit the patients, but logistics in terms of timing related to transplantation, compliance, and access to the intervention are challenging.	• Incorporate mixed methods research to explore factors contributing to barriers for implementing interventions for frailty in these populations, including interventions on environmental factors and social determinants of health

understanding of frailty in the PTx candidate and how those findings should influence patient selection. PTx programs should consider a multidimensional strategy for frailty testing through FFP and SPPB, as both are well validated and SPPB provides a robust objective approach.

Although an exact frailty cutoff for PTx is not defined, providers may offer kidney transplantation alone and if success is met consider a pancreas after kidney transplantation. Certainly, many such patients could be best suited with a SPK from the start, but for cases where frailty is a compelling concern the use of kidney transplantation alone may be prudent and can serve as a barometer for tolerance of a future PTx. Further study is needed to substantiate this practice and we endorse SPK when nutritional, cardiovascular, and pulmonary risk profiles are acceptable, given the superior long-term opportunity for both dialysis and insulin independence.[170]

Overall, frailty is a known risk factor for unfavorable waitlist and post-transplant outcomes and its detection has been shown to limit access to kidney transplantation. Despite the paucity of PTx specific intervention studies, comprehensive exercise training programs are likely a significant mitigator of frailty before and after PTx. The potential for dynamic change in frailty after PTx needs great investigation as improvement in frailty over time could provide opportunity to limit poor outcomes. As further research becomes available PTx candidates and recipients will benefit from our improved understanding of frailty and its pathogenesis, measurement, and treatment (Box 1).

Furthermore, PTx may still be indicated in patients who have developed frailty. Patients with insulin dependent DM can fail medical therapy resoundingly, whether for reasons related to physiologic response

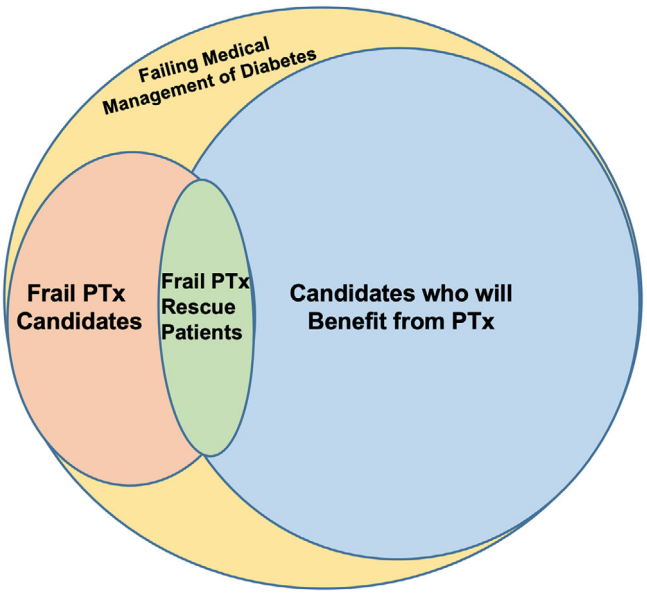

FIGURE 3 Diagram of diabetes patient populations failing medical management who may have frailty and may benefit from PTx

to intermittent exogenous insulin, health literacy, social determinants of health or caregiver fatigue. Such patients experiencing deconditioning and failure to thrive will often meet criteria for frailty. Nonetheless, after careful multi-disciplinary assessment a population of these frail patients will meet criteria for PTx and can derive substantial benefit (Figure 3).

Transplant providers and public health advocates need to build robust policy which increases the likelihood for early access to PTx to minimize the consequences of prolonged diabetes and frailty. Future research should also focus on what degree of frailty predicates futility when implementing PTx as a rescue therapy.

ACKNOWLEDGMENT

None.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Parsons RF, Tantisattamo E, Cheungpasitporn W, et al. Comprehensive review: Frailty in pancreas transplant candidates and recipients. *Clin Transplant*. 2023;37:e14899. https://doi.org/10.1111/ctr.14899