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Review article

Gray-scale, Doppler and contrast-enhanced ultrasound in pancreatic allograft surveillance: A systematic literature review

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ABSTRACT

Background: Gray scale ultrasound (US), Doppler and Contrast Enhanced Ultrasound (CEUS) represent important surveillance tools in the early post-operative period after pancreas transplantation (PTx), when complications are more common. This review summarizes the available evidence on their clinical application in this setting.
Methods: We searched the Pub-Med database from inception to October 2018 for English literature on the clinical use of US, Doppler and CEUS in the post-PTx surveillance. Article selection was carried out according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses criteria (PRISMA).
Results: Twenty-nine articles concerning the clinical applications of US, Doppler and CEUS were identified, 13 of which, involving 264 patients, were focused on the sonographic findings in immunologic rejection, whereas 11 studies reporting on 887 patients were focused on post-PTx vascular complications. The remaining five articles, involving a total of 196 patients, described US or CEUS applied in the study of pancreatic morphology and texture to diagnose peri-graft fluids collections or to obtain experimental data on allograft endocrine function.
Conclusions: US, Doppler and CEUS have proven to be valuable assets in post-PTx follow up, thanks to the combination of their non-invasiveness with a high accuracy in the detection of early abnormalities, in particular regarding vascular complications. Preliminary experiences are directing towards functional research; however, future prospective trials are necessary to precisely correlate organ perfusion, early abnormalities and allograft function.

Contents

1. Introduction

The goal of pancreas transplantation (PTx) is to improve the outcomes and the quality of life of many patients affected by type 1 diabetes, achieving an independence from insulin injection. In addition, in the

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last years, this therapeutic approach is also increasing in patients with type 2 diabetes [1]. Although the number of PTx in the United States has decreased from 2004 to 2015, in 2016 a 7% increment was registered, mainly due to the increase of simultaneous pancreas-kidney transplantation which represents the main indication in patients with end stage diabetic renal disease. Despite important advantages in surgical technique and immunosuppression regimes in the last decades, this complex operation is still associated with various complications that contribute to reduce both patient and graft survival rates [2]. A spectrum of adverse events includes: graft rejection, vascular problems, peri-pancreatic collections, infections and haemorrhages. To date, neither clinical or laboratory markers can precisely define pancreatic graft dysfunction nor biochemical tests allow immunological rejection to be distinguished from vascular occlusion [3]. Moreover, vascular or immunological damages tend to be initially silent and to become evident only when most of the parenchyma is injured, precluding the possibility of pancreatic allograft rescue. Therefore, it is very important to improve the imaging surveillance, especially during the first post-transplant week, where thrombosis is more common [4]. In this setting, gray-scale ultrasound (US) represents a real time, bed-side and non-invasive exam capable to detect fluid collections and to evaluate the pancreatic morphology. Moreover, the Doppler function (Pulse Doppler, Color-Doppler, Power-Doppler and Spectral analysis) allows to investigate the blood flow. The advent of Contrast Enhanced Ultrasound (CEUS) is particularly suitable for vascular study [5] in this setting as it avoids the main drawbacks of Magnetic Resonance (MR) or Computer Tomography (CT) related respectively to the not always prompt availability and to the use of potentially nephrotoxic contrast agents.

The aim of this study is to summarize the available evidence on the current status of US and CEUS in the post-PTx surveillance and to assess their clinical application, analysing benefits and limitations.

2. Methods

A literature review was accomplished from inception to October 2018 using PubMed database for English literature. The searched formulas were: “ultrasound in pancreas transplantation”, “ultrasound pancreatic transplantation surveillance”, “ultrasound pancreatic transplantation follow-up”, “sonography pancreatic transplantation surveillance”, “sonography pancreatic transplantation follow-up”, “contrast-enhanced ultrasonography in pancreas transplantation”. We selected only articles where authors described the clinical utility of US, Doppler sonography and/or CEUS in the post-PTx outcome. Article selection was carried out according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses criteria (PRISMA) [6] (Fig. 1). Manuscripts identified by cross-referencing were also retrieved and evaluated. Editorial comments, letter to the editor or indexed abstracts at International Congress were not considered. Studies describing the importance of other imaging modalities in PTx, overviews or works without clinical records were also excluded. We extracted from each study the following data: number of patients, type of transplant (pancreas transplant alone -PTA, simultaneous pancreas-kidney transplants -SPK, simultaneous cadaveric pancreas living kidney transplants -SPLK, pancreas after kidney transplant -PAK), type of exocrine drainage (bladder or via entero-entero anastomosis), type of vascular complication with particular attention to thrombosis, US technical description, resistive index (RI), intensity curve for CEUS, presence of biopsy for suspected rejection or second-level imaging results. Three authors (SG, MP and NF) independently reviewed all the manuscripts that met the inclusion criteria. The final search was completed by 15 December 2018.

3. Results

Twenty-nine articles focusing on the role of US, Doppler or CEUS in PTx surveillance were included in the review. The included studies were divided in three main groups according to the field of application of US: detection of graft rejection, identification of vascular complications and other information. We found thirteen studies [7–19] reporting on 264 patients mainly focused on the sonographic findings in immunologic rejection. Most of transplants were SPK (127 cases, 48%), with bladder drainage as the most used technique (9 articles, 62% of total) till 1996. In the field of vascular complications, we found eleven articles [20–30] reporting on 887 patients, 494 of which were SPK (55% of total) and venous thrombosis was the first vascular problem described in 7 manuscripts (63% of total). The remaining five articles [31–35] reporting on a total of 196 patients, were focused on the organ morphology/texture or peri-pancreatic collections (four papers) and the allograft function (one paper).

1. US, Doppler and CEUS in the detection of pancreatic allograft rejection (Table 1)

The first studies about the importance of Doppler signal in PTx were conducted in 1988 by Gilabert et al. [7] and Kubota et al. [8] who reported a certain helpful of US and Doppler in the diagnosis of pancreatic allograft rejection. In the same year, Patel et al. [10] showed a correlation between RI and early detection of pancreatic rejection in 22 patients underwent SPK. A cut off value of 0.7 was found with a 100% positive predictive value and a 90% negative predictive value. The main limitation was the lack of pancreatic allograft biopsy, assuming as reference a concomitant kidney rejection. In 1991 Batiuk et al. [11] correlated pathological data with the US evaluation of pancreas morphology and density, without using RI. They concluded that US has a sensitivity of 57% and a specificity of 67% for the diagnosis of graft rejection. Conversely, in 1991, Milner et al. [12] firstly found that RI was not so useful in case of suspected rejection, studying three patients with 20 separate examinations, which had no RI significant changes in case of rejection. In 1992, another study conducted by Gilabert et al. [13] on 22 patients reported a higher RI in rejection’ patients versus normal allografts.

In 1995 Wong et al. [15] presented their prospective clinical trial correlating transplant histological findings with US pancreas morphology, eco-texture and RI. In a cohort of 36 patients with clinical and laboratory findings suspected for PTx rejection underwent US and Doppler within 48 h from percutaneous pancreatic biopsy, they found a low specificity and sensibility for elevated RI (cut off >0.70). Quite interesting to note that the gland enlargement and the heterogeneity of eco-texture had a specificity of 100% but occurred later in the rejection process. Along the same line, Aideyan et al. [16] concluded that RI failed to predict the milder forms of rejection and also to distinguish non-severe forms of rejection from absence of rejection because so much overlap existed in the RI of these groups. In 1996 Nelson et al. [17] reviewed 79 cistoscopically directed trans-duodenal pancreatic allograft biopsies performed in a mean 8.6-month period in order to investigate the value of RI as an absolute level or a relative increase. Again, they suggested that increases in the RI over baseline values are poor predictors for acute rejection but may play a role in chronic rejection in which stable fibrosis lead to an increased vascular resistance.

More recently, Gimenez et al. [18] described a specific US protocol that assess the allograft in B-Mode and Doppler, evaluating the splenic pedicle and obtaining RI in all the pancreatic parts in a reproducible manner (96% of visualization). In a population of 52 patients, they found that when RI was >0.75 any type of complications might have occurred, whereas in presence of a RI value of 0.9, rejection might have been seriously considered.

The only article reporting on the use of CEUS in the evaluation of the immunologic damage of pancreas allograft was published by Kersting et al. [19] in 2013, describing a series of 14 patients in which an ultrasound biopsy was performed in every case of rejection. The authors confirmed the low sensitivity of RI alone, but they also reported that CEUS, using time intensity curves, was able to evaluate an early rejection

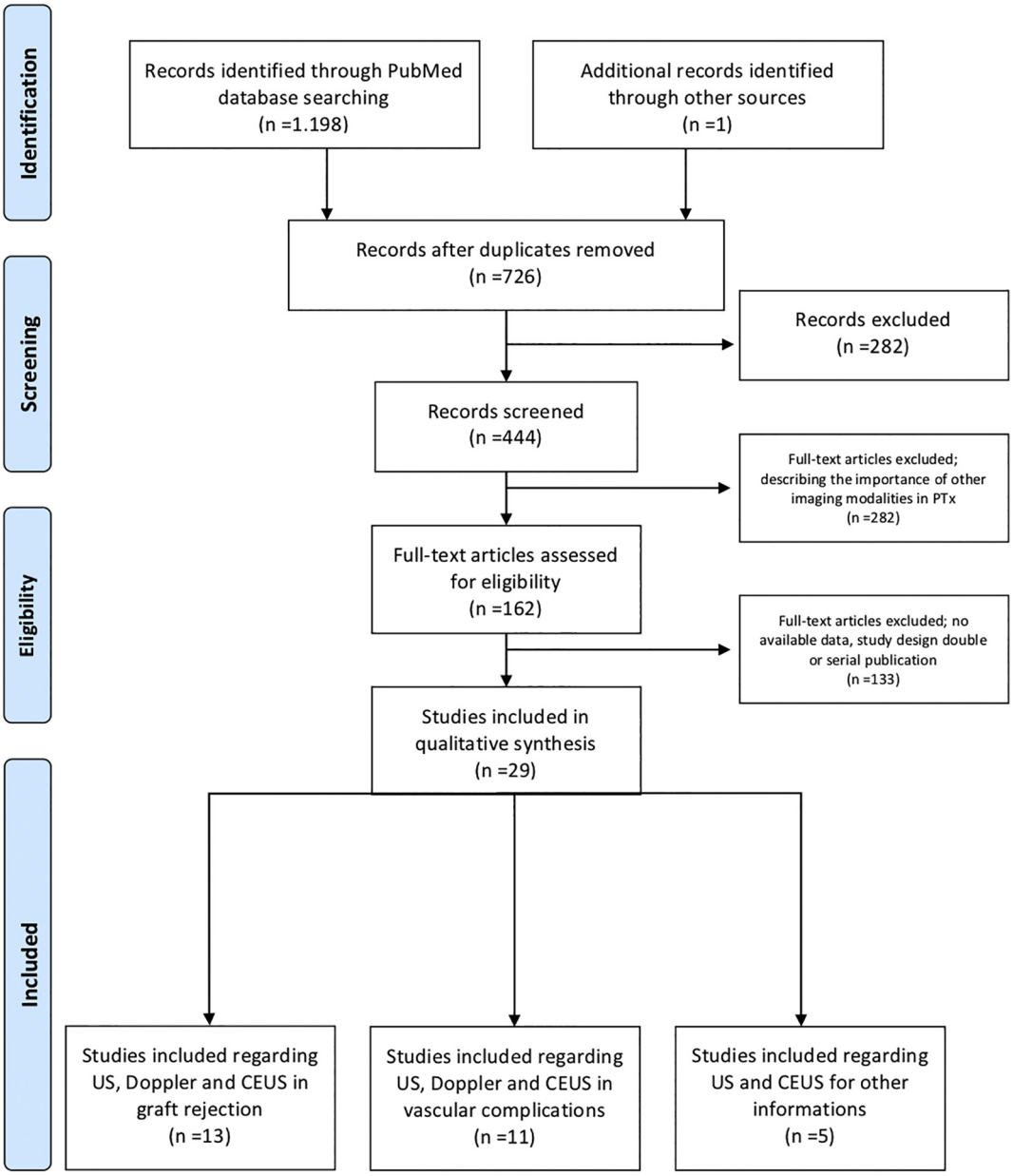

Fig. 1. Flowchart of our literature review.

episode because it exhibited significantly diminished maximum contrast intensity and a slower increase to reach this maximum.

2. US, Doppler and CEUS in the detection of vascular complications (Table 2)

The description of quantitative measures of pancreas allograft circulation was firstly performed by Yang et al. [20] in 1990. In the same year, Boiskin et al. [21] published a case report of a SPK venous graft thrombosis, describing suspected Doppler findings such as the absence of venous outflow and a short systolic waveform in the splenic artery. Due to the failure to visualize the pancreas allograft at scintigraphy, the diagnosis was venous graft thrombosis and due to the worsening of clinical picture, the patient underwent surgical exploration. The pathological exam confirmed organ infarction and splenic plus portal thrombus. In 1991, Snider et al. [22] reported their experience with US and Doppler in 35 cases. The authors investigated the accuracy of Scintigraphy, CT and US in discovering graft thrombosis in patients that subsequently underwent graft pancreatectomy or angiography. The main inconvenience was the lack of specificity of gray scale abnormalities meanwhile Doppler appeared promising in detecting this type of complication. In 1995 Nghiem et al. [24] underlined the importance of Doppler in the early assessment of venous thrombosis which was usually diagnosed so late that pancreatectomy represented the only possible option. Thanks to the decreased splenic vein flow rate evaluated with Doppler and to the reduction of urinary amylase, they were able to attempt graft trombectomy in the early outcome. In 1996, Foshager et al. [25] also published their experience with 45 patients divided in two groups: the study population which consisted in surgically documented allograft thrombosis cases (11 patients) and the control group composed by patients followed with Doppler within 12 days after PTx (34 cases). They demonstrated that the diastolic flow reversion associated with the absence of detectable venous signal inside the organ presented high specificity and sensibility for venous graft thrombosis in the early post-operative surveillance. In 2008, Morelli et al. [26] confirmed in a study sample of 223 patients the essential role of Doppler in providing early information about vascular abnormalities of transplanted pancreas and identifying the need of immediate

Table 1
Summary of articles regarding US in pancreatic allograft rejection.

Author (year)	N Patients involved	Exocrine drainage	US method	Biopsy	Number of exams	RI
Gilabert R (1988) [7]	7; 3 SPK	BD	Gray scale; Doppler	No	42	N 0.61–0.68 R 0.70–0.89
Yuh WT (1989) [9]	17	BD	Gray scale	No	12	
Patel B (1989) [10]	22 SPK	BD	Gray scale; Doppler	No	115 US 98 Doppler	N 0.59 ± 0.06 R 0.79 ± 0.08 Cut off 0.70
Kubota K (1990) [8]	9	ED	Gray scale; Doppler	No	NS	N 0.53–0.76 R 0.62–0.75
Batiuk T (1991) [11]	14	BD	Gray scale	Yes	NS	
Milner L (1991) [12]	3; 1SPK, 2 PTA	BD	Gray scale; Doppler	No	20	N 0.71 ± 0.12
Gilabert R (1992) [13]	22	BD	Gray scale; Doppler	No	NS	N 0.63 ± 0.006 R 0.75 ± 0.03
Lang H (1996) [14]	9 SPK	ED	Doppler	No		N 0.69 $R > 0.80$
Wong J (1996) [15]	36; 21 SPK, 12 PAK, 3 PTA	BD	Gray scale; Doppler	Yes (51) PC	51	N 0.67 ± 0.07 R 0.64 ± 0.08
Aideyan A (1996) [16]	20	BD	Doppler	Yes (17) 9C, 8PC	NS	N 0.64 ± 0.1 R ML 0.66 ± 0.0 R MD 0.67 ± 0.06 R SV 0.85 ± 0.07
Nelson N (1996) [17]	40; 19 SPK, 21 PTA	BD	Doppler	Yes (78) C	NS	N 0.65 ± 0.07 R ML 0.64 ± 0.06 R MD 0.63 ± 0.09 R C 0.72 ± 0.1
Gimenez J (2012) [18]	51 SPK	ED	Doppler	No	204	N 0.65 ± 0.09 R 0.94 ± 0.09
Kersting S (2013) [19]	14; 10 SPK	ED	Doppler, CEUS	Yes (4) PC	42	N 0.70 ± 0.09 R 0.74 ± 0.06

Abbreviations: SPK, simultaneous pancreas-kidney transplants; PTA, pancreas transplant alone; PAK, pancreas after kidney transplant; BD, bladder drainage; ED, enteric drainage; PC, percutaneous biopsy; C, cistoscopic biopsy; RI, resistive index; N, normal; R, rejection; R ML, mild rejection; R MD, moderate rejection; R C, chronic rejection; NS, not specified.

treatment. In 28 cases Doppler suspected venous graft thrombosis that was confirmed with a second level imaging in 75% of these patients. In 18 patients, a graft rescue was attempted and successfully concluded in 77% of cases thanks to quick diagnosis and prompt management (arterial fibrinolysis, heparin infusion or surgical trombectomy). In a study evaluating early re-exploration for suspected graft thrombosis, Fridell et al. [27] found Doppler to present a sensitivity of 55%, a specificity of 53%, a positive predictive value of 61% and a negative predictive value of 47% in this setting. In 2016 Morgan et al. [28] took in consideration the value of US edema, splenic vein thrombus and reversal arterial diastolic flow as factors associated to an increased risk of graft failure, in a cohort of 228 PTx monitored with US. In a multivariate modality, only reversal or absent arterial flow identified a subgroup with a reduction of organ survival. They presumed that the presence of a venous thrombus may be checked in asymptomatic patients with US, but this was not necessarily associated with altered perfusion and might solve during the follow up. Instead, associated arterial reversal flow defined an increased vascular resistance and enabled direct assessment of pancreatic parenchyma perfusion.

The first article describing CEUS as an additional modality for PTx vascular complications detection was published in 2009 by Boggi et al. [29]. In this case report, Doppler and CT scan were concordant about

Table 2
Summary of articles regarding US in vascular complications.

Author (year)	N Patients involved	Type of vascular complication	US method	Second level imaging/Surgery	Number of exams	Comments
Yang HC (1990) [20]	2 SPK		Gray scale; Doppler		NS	Utility of Doppler in evaluating allograft' perfusion
Boiskin I (1989) [21]	1 SPK	VT	Gray scale; Doppler	Surgery	NS	Increased vascular resistance, absence of venous outflow
Snider J (1991) [22]	22	AT, Others	Gray scale; Doppler	Arteriogram, Surgery	27 US, 8 Doppler	
Nghiem DD (1994) [23]	7	VT	Doppler	Surgery		SVv mean 6.7 cm/s in VT
Nghiem DD (1995) [24]	3	VT	Doppler	Surgery	54	↓ SVv
Foshager M (1996) [25]	45; 23 SPK, 15 PAK, 7 PTA	VT	Doppler	Surgery	54	ADR, RI; N 0.72 ± 0.18 T 1.31 ± 0.29
Morelli L (2008) [26]	223; 115 SPK, 27 SPLK, 66 PTA, 15 PAK	AT, VT	Doppler	CT, Arteriogram	NS	
Boggi (2009) [29]	1	AT	CEUS	CT	1	
Fridell (2011) [27]	345; 185 SPK, 85 PKA, 75 PTA	AT, VT	Doppler	Surgery	NS	Se 55%; Sp 53%
Rennert J (2014) [30]	10	AT, VT	CEUS	CT, MR, Arteriogram	NS	
Morgan T (2016) [28]	228; 170 SPK, 38 PAK, 20 PTA	VT	Gray scale; Doppler	Surgery, Clinical	786	ST: Se 27%; Sp 83% ST + ADR Se 23%; Sp 91%

Abbreviations: SPK, simultaneous pancreas-kidney transplants; PTA, pancreas transplant alone; PAK, pancreas after kidney transplant; AT, arterial thrombosis; VT, venous thrombosis; RI, resistive index; SVv, Splenic vein velocity; ADR, arterial reverse diastolic flow; Se, sensibility; Sp, specificity; NS, not specified.

the complete occlusion of the donor's superior mesenteric artery without tissue enhancement in the pancreatic head. The patient was scheduled for re-laparotomy; however, before surgery a CEUS examination was performed showing tiny collateral vessels for the head with a homogeneous parenchymography after 90 s. The therapeutic decision was turned to conservative management and surprisingly the patient's general condition and the graft status improved. At an 18 month follow up the patient achieved insulin independence and the graft presented a homogeneous parenchymography. With a bigger population, Rennert et al. [30] described the use of CEUS with pulse inversion harmonic imaging mode in pancreas-kidney transplantation and confirmed the important and additional information provided by this method in patients with early vascular complications. They concluded that CEUS was well tolerated, reproducible and, in selected cases, was able to obviate the need of CT or MR.

3. US and CEUS for other information (Table 3).

In 1982 Toledo-Pereyra et al. [31] described their preliminary experience using US in the post-operative period of 5 patients underwent PTx. They considered the gland size, the internal texture and the presence of peri-graft collections trying to discover any deviation from normal appearance. In 1987 Letourneau et al. [32], underlined the importance of US primarily in the detection of several type of peri-pancreatic collections e.g. lymphocoele, abscess or haematoma in a series of 141 cases studied with US and CT. In 1988 Patel et al. retrospectively analysed the importance of US, scintigraphy and CT in PTx complications [33]. They described certain US "pancreatic pattern" such as organ enlargement, multiple anechogenic areas with rejection, oedematous pancreas, dilated main duct and fluids surrounding the organ with pancreatitis concluding that early US should be performed when scintigraphy scans are abnormal. In 1996, Stafford-Johnson et al. [34] described 22 US and Doppler examinations performed in SPK patients and concluded that sonography represents the most useful method for the initial assessment of both kidney and pancreas allografts as it assesses organs measurement and consistency and it can detect fluid collections and vascular patency.

The first report correlating CEUS quantitative data with pancreatic allograft function, with regard of its endocrine counterpart, was recently published by Aida N et al. [35] (2018). They performed serial post-Tx CEUS exams in 17 patients calculating the time difference in peak intensity between the pancreatic parenchyma and the portal vein as an index of micro-circulation. The endocrine graft function was tested using the glucagon stimulation test and the oral glucose tolerance test 1 month after transplant. They demonstrated that CEUS parameters are related to ischemia-reperfusion injury and negatively affect graft insulin secretion at 1 and 3 months.

4. Discussion

Despite the advent of emerging alternatives such as the islet cells transplantation [36] and the artificial pancreas [37], PTx remains a valid option in patients affected by diabetes. The success rates of this transplant have improved with the increased experience of the transplantation teams with the management of the recipients. In the United States, five-year patient survival rates are currently 93% for SPK, 91% for PAK, and 78% for PTA recipients, whereas the graft survival rates are currently: 73% for SPK, 65% for PAK, and 53% for PTA [38]. However, this procedure is still associated with a high rate of surgical and immunological complications. The incidence of rejection ranges from 14 to 21% during the first-year post-transplantation [39]. Risk factors seems to be non-primary SPK transplants, primary PTA, race mismatch, and increased donor age, although the latter has been expanded in many transplantation centres with satisfactory results [40]. From a surgical standpoint, during the early post-transplant period a re-laparotomy is required with a frequency ranging from 14% to 65% and vascular thrombosis represents the main cause [41], with an estimated venous thrombosis rate of 5%. This is in part related to technical problems but also to the systemic influence of chronic diabetes, the intrinsically low blood flow to the pancreatic allograft and the susceptibility to ischemic reperfusion damage. Since the diagnostic value of physical examination is quite limited and no single chemical marker has allowed rejection to be distinguished from vascular problems, a diagnostic imaging is necessary. Despite their high accuracy, CT and MR are not immediately and always available and cannot be used for surveillance due to several reasons. In this scenario, US was extensively used in the post-transplant period with other solid organ transplantation such as liver and kidney, thanks to its versatility.

This work has mainly reviewed the two main fronts about the utility of sonography in the early evaluation of PTx considered in literature: allograft rejection and vascular problems. US alone, evaluating pancreas graft dimension and echo-structure, is highly sensible for allograft pathology but has a poor specificity for differential diagnosis, so that Doppler exam should be always performed. Furthermore, although duodenal oedema could be theoretically associated with acute rejection as well as other issues such as ischemic re-perfusion injury or pancreatitis, we weren't able to find data on the possible role of this specific findings in the revised literature.

Early detection of PTx rejection remains elusive, particularly in absence of simultaneous kidney transplantation. The considered studies covered a wide range of time with different surgical techniques used both for exocrine and venous outflow. The advantages of pancreas-bladder drainage included the possibility to monitor urinary amylase levels which are more sensible respect to blood exams and to perform biopsies throughout cystoscopy. However, severe urinary tract infections, metabolic disorders and graft inflammations represented important drawbacks so that the enteric drainage has become predominant over time [42]. In this situation, the evaluation of serum markers is the only way forward and in case of suspected rejection, only the percutaneous way is possible for biopsy.

In addition, modern Doppler equipment and high performant US machines available in recent works respect to the first ones, contribute to affect the discordant results. In fact, preliminary reports without histological comparison have found US and Doppler to be substantially helpful whereas other studies that used biopsy as a benchmark questioned about the absolute importance of US and Doppler in

Table 3
Summary of articles regarding US in PTx: Other information.

Author (year)	N Patients involved	Main issue	US method	Number of exams	Comments
Toledo-Pereyra LH (1982) [31]	5 PTA	Morphology	Gray scale	NS	Organ size, internal structure, peri-graft collections.
Letourneau JG (1987) [32]	141	Morphology	Gray scale	NS	Peri-pancreatic collections
Patel B (1988) [33]	21 SPK	Morphology	Gray scale	112	Organ size, internal structure, peri-graft collections.
Stafford-Johnson DB (1996) [34]	12 SPK	Morphology	Gray scale; Doppler	22	Organ size, internal structure, peri-graft collections, vascular patency
Aiada N (2018) [35]	17; 12 SPK, 5 PAK	Endocrine function	CEUS	119	Micro-circulation affects graft insulin secretion

Abbreviations: SPK, simultaneous pancreas-kidney transplants; PTA, pancreas transplant alone; PAK, pancreas after kidney transplant; NS, not specified.

pancreatic rejection. Improved technology and dedicated surveillance programs contribute to define a RI normality range with only a minimal overlap in pathological cases. Gimenez et al. [18] supported that when RI was <0.65, aside fluid collections, the risks of pathologies was very low, while when RI was >0.75 vascular problems, pancreatitis or rejection should be suspected, with the highest RI value in case of rejection. The lack of biopsy certainly invalidated the relationship between RI and both acute or chronic rejection, but the strength of this manuscript is related to the importance of sonography in the routinary assessment of PTx patients. Doppler evaluation should be contextualized with physical exam plus other diagnostic modalities because RI absolute or relative values alone are non-specific indicators of rejection. Indeed, despite the fewer conditions other than rejection that may modify vascular resistance in PTx respect to kidney transplant, the absence of a strong capsule in pancreatic allograft alters the parenchymal pressure during rejection and consequently the impedance of vascular bed.

In this context, CEUS seems to add more information giving a fundamental support in the diagnostic yield. CEUS is a dynamic and non-invasive method that investigates microscopic vessels and perfusion throughout microbubbles oscillations. Specific software is also available to quantify changes in contrast intensity giving quantitative parameters. The capillary perfusion may be impaired in the early phase of rejection and this phenomenon is well detected by CEUS because there is a trend towards a reduction of contrast agent in the region of interest and a longer time to peak value respect to the normal status. The study conducted by Kersting et al. [19] has demonstrated that contrast exam is more sensitive than Doppler alone in PTx rejection because CEUS directly reflects every microcirculation abnormality and it is not related to the elasticity and the upstream capacity of large vessels like RI. However, as other conditions such as pancreatitis may change quantitative CEUS parameters in a similar manner, currently biopsy remains the gold standard approach to rule out pancreatic rejection.

Unlike suspected rejection, there is a unanimous consensus aboutthe importance of US and Doppler in the early detection of PTx vascular complications, particularly thrombosis. The rationale is to prevent the progression to organ infarction making allograft removal mandatory. In addition, systemic response to necrotic factors, pulmonary embolism or pancreatitis are sequels that can cause patient's death.

Venous thrombosis was largely evaluated in literature, representing the more common and detectable vascular complication. It is quite interesting to note that the presence of a venous thrombus is frequent in the post-surgical period, with an estimated frequency of 17% in asymptomatic patients [43], more commonly involving the splenic vein, close to the pancreatic tail. This may be related to the blood stagnation at this level and the cold ischemic damage of the endothelium. The thrombus can partially or completely occlude the vessel but the presence of the thrombus alone represents a poor indicator of graft failure and its clinical relevance is not extensively evaluated yet [27]. The dilemma in this situation is to precociously treat the thrombosis with high dose of anticoagulants or with surgical evacuation in order to prevent graft failure. The early systemic anticoagulation may increase the haemorrhagic risk and consequently require an emergency surgery. On the other side, the price for a negative explorative laparotomy in case of well vascularized organ potentially reduces graft survival due to the unnecessary surgical stress [44]. Doppler evaluation seems to give a fundamental value in order to identify patients with increased risk of PTx failure in case of venous thrombosis and permits a tailored treatment, potentially enhancing allograft function and minimizing treatment-related morbidity. The first studies posed the attention mainly to the venous outflow. However, the lack of this signal may be related to technical problems rather than the real absence of flow; indeed, PTx Doppler is notoriously challenging and slow flow is often difficult to detect. Instead, the arterial reversal flow seems to be the most reliable sign correlating to vascular impedance and organ perfusion. This abnormality is considered highly predictive of organ failure by several studies, such as by Morgan et al. [28]. It is also quite specific because in severe rejection, although RI is very high, a certain forward diastolic flow is usually present. Moreover, in case of other pathologies intra-parenchymal veins are patent.

Furthermore, the use of contrast agent adds important value in the management of vascular complications. In fact, CEUS can be employed to recognize minimal tissue perfusion concerns in case of vascular thrombosis when other imaging modalities have failed, thanks to its real-time blood-pool behaviour. CEUS provides additional clinically relevant information that can obviate CT or MR or modify the therapeutic management and may be used to monitor any changes in micro-vascular distribution with repeated examinations.

To the best of our knowledge, this is the first article that fully reviews the adequacy of US, Doppler and CEUS in the PTx surveillance. In conclusion, these exams appear to be valuable assets in PTx, thanks to the combination of their non-invasiveness with a high accuracy in the detection of early abnormalities, in particular regarding vascular complications. This simplifies the recognized issues of other radiologic imaging, such as difficult access, not immediate availability and the need of contrast agents. The several advantages of sonography early discovered in 1990's was subsequently developed and its adoption has increased. We are quite far from a direct correlation between a sonographic finding and a specific pancreatic graft pathology but its contribution together with clinical assess and chemical data can guide the transplantation teams to the optimal management. If this contribution is less important in immunologic reactions where the biopsy remains the procedure of choice (do not forget that the biopsy in portal-enteric drainage is performed percutaneously using US as a guide to reduce risks [45]), in vascular complications sonography gives reliable diagnostic and prognostic details. In fact, US can discover pseudo-aneurysms, fistulas, stenosis and, more important, vascular thrombosis and to identify a subgroup of patients with a higher risk of allograft failure. In addition, particularly with the aid of CEUS, we surpass the limits of other imaging examinations allowing a personalized treatment in order to increase the chances of graft survival. At the moment, general limitations of sonography are: operator-dependent modality and patient's habitus and bowel distention that may preclude a complete study. PTx surveillance with US and Doppler implies an extensive knowledge of surgical procedure and pancreatic disorders and should be performed in specialized center. Improvements may come from the advancing technologies [46], such as sensible Color-Power Doppler, super resolution imaging, three-dimensional visualization, elastosonography and new contrast agents with specific software. The “functional imaging” in which the morphologic appearance of a certain organ is integrated with metabolism, blood flow and chemical composition is developing nowadays and even in the field of transplantation CEUS seems to be a very good stepping stone. Preliminary reports have just underlined the superior abilities of CEUS in assessing pancreatic allograft at back-table before transplantation [47] or in defining endocrine function. In fact, Aiada et al. [35] have recently found that CEUS may discover early disorders related to ischemia-reperfusion injury and affecting allograft insulin secretion even at 3 months after PTx. Prospective trials with big samples should evaluate pancreatic micro-vascular changes as predictors of a specific alteration, discover factors that may influence these changes and correlate them with graft mid-term function.

Conflict of interests

The authors declare that there is no conflict of interest. No founding.

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