

## A steady decline in pancreas transplantation rates

Stan Benjamens<sup>a, b, \*</sup>, Marjolein Leemkuil<sup>a</sup>, Christian Margreiter<sup>c</sup>, Volkert AL. Huurman<sup>d</sup>, Henri GD. Leuvenink<sup>a</sup>, Robert A. Pol<sup>a</sup>

<sup>a</sup> Department of Surgery, Division of Transplantation Surgery, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

<sup>b</sup> Medical Imaging Center, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

<sup>c</sup> Department of Visceral, Transplant, and Thoracic Surgery, Medical University of Innsbruck, Innsbruck, Austria

<sup>d</sup> Department of Surgery, Leiden University, Leiden University Medical Center, Leiden, the Netherlands

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### ABSTRACT

**Background/objectives:** After years of growth in many pancreas transplant programs, UNOS has reported declining transplant numbers in the USA. This precipitating trend urges for an evaluation of the transplant numbers and scientific productivity in the Eurotransplant region and the UK.

**Methods:** We performed a trend analysis of pancreas transplantation rates, between 1997 and 2016, adjusting for changes in population size, and an analysis of scientific publications in this field. We used information from the UNOS, Eurotransplant, and UK transplant registry and bibliometric information from the Web of Science database.

**Results:** Between 2004 and 2016 there was an average annual decline in pancreas transplantation rates per million inhabitants of 3.3% in the USA and 2.5% in the Eurotransplant region. In the UK, transplant numbers showed an average annual decline of 1.0% from 2009 to 2016. Publications in Q1 journals showed an annual change of  $-2.1\%$  and  $+20.1\%$ , before 2004, and a change of  $-3.8\%$  and  $-5.5\%$ , between 2004 and 2016, for USA and Eurotransplant publications, respectively.

**Conclusions:** Adjusting pancreas transplantation rates for changes in population size showed a clear decline in transplant numbers in both the USA and Eurotransplant region, with first signs of decline in the UK. Following this trend, the number of scientific publications in this field have declined worldwide. © 2018 IAP and EPC. Published by Elsevier B.V. All rights reserved.

### Introduction

Pancreas transplantation is currently the only treatment option that ensures normal glucose metabolism in the long term in patients with a high risk of diabetes mellitus (DM) complications [1,2]. After several years of growth in many pancreas transplant programs, the United Network for Organ Sharing (UNOS) has reported a decline in transplant numbers in the United States (USA) [3–5]. Although a few papers do address the reasons for this decline, there is currently no literature on the effect of this decline on high-quality publications [4,6]. A recent overview publication in the BMJ, by Dean et al., describes a gap in knowledge and concludes that further studies are needed to enable more patients to benefit from this treatment option [7]. The authors also address the need

for multicentre trials in pancreas transplantation to more clearly define the efficacy, risks, and long term benefits. Additionally, the literature shows a telling difference in pancreas transplantation activity between Europe and the USA [8]. All the aforementioned calls for an evaluation of the transplant numbers and scientific productivity in the Eurotransplant region and the United Kingdom (UK), and for repeated comparison of transplant activity between Europe and the USA.

The primary objective of this study is to present the changes in pancreas transplantation rates in the USA, Eurotransplant region, and the UK; using the UNOS database, the Eurotransplant registry, and the UK Transplant Registry [9–11]. To put these numbers in perspective, we evaluated the prevalence of type 1 DM and C-peptide positive DM in these regions. As a secondary objective, we performed a bibliometric analysis of scientific publications on pancreas transplantation, to examine whether the publication trends show parallels with the pancreas transplantation rates.

\* Corresponding author. Department of Surgery, Division of Transplantation Surgery, University Medical Center Groningen, P.O. Box 30 001, 9700 RB, Groningen, the Netherlands.

E-mail address: [s.benjamens@umcg.nl](mailto:s.benjamens@umcg.nl) (S. Benjamens).

## Materials and methods

To evaluate the need for pancreas transplantations, the age-standardized C-peptide positive DM prevalence in the USA, Eurotransplant region, and the UK are presented. These outcomes are based on the multi-analysis of 751 population-based studies (1980–2014) performed by the NCD Risk Factor Collaboration [12]. The average prevalence of DM for the Eurotransplant region was calculated and adjusted using the population size of each country. The type 1 DM incidence rate per 100,000 children, ranging from 0 to 19 years of age, is based on the International Diabetes Federation (IDF) Diabetes Atlas (8th edition, 2017) and the related scientific publications [13–16].

We used the UNOS database, Eurotransplant registry, and the UK transplant registry to describe the development of pancreas transplantation rates between 1997 and 2016 [9–11]. Transplantation rates were adjusted for changes in population size in the different regions, using demographic statistics from the United States Census Bureau, Eurostat, and the Office of National Statistics United Kingdom [17–19].

To perform a bibliometric analysis, we used the Web of Science database with the term “pancreas transplantation” to include all relevant publications between 01 and 01–1997 and 12–31–2016 [20]. We focused on original publications, written in the English language, and excluded editorials, letters to the editor and conference abstracts. We selected journals from the categories “Transplantation”, “Surgery”, “Medicine”, and “Endocrinology”, and stratified our results in accordance with the 4 quartiles (Q1–Q4), based on the journals’ impact factor (IF) [21]. Additionally, articles with over 100 citations were selected to describe the advancements in pancreas transplantation during the search period.

All data was analyzed using GraphPad Prism version 6 (GraphPad Software, Inc., USA, 2012). Results are presented with descriptive statistics and linear scaled graphs or using bar graphs. To assess the development of pancreas transplantation and publication rates, a graph specific slope was calculated using linear fitting of changes in the number of transplantations and publications over time. Formulas generated by linear fitting are provided for the population adjusted number of pancreas transplantations, and the number of publications.

## Results

### Diabetes prevalence

From 2000 to 2014, age-standardized adult DM prevalence showed an increase for males in the USA (7.0% to 8.2%), Eurotransplant region (5.6% to 6.1%), and the UK (5.9 to 6.6%) (Fig. 1). For females, the increase was significantly lower with a 5.7% to 6.4% increase in the USA, 4.0% to 4.1% in the Eurotransplant region and 4.8% to 4.9% in the UK [12]. Overall, 95% of all cases of DM are C-peptide positive DM, which in most literature is referred to as type 2 DM [22].

In the USA, the incidence of type 1 DM per 100,000 children between 0 and 19 years of age, increased from 19.5 to 21.7, between 2002 and 2012 [23]. In the Eurotransplant region (subdivided by participating country), the incidence rates per 100,000 children between 0 and 15 years of age increased from: 9.0 to 17.5 in Austria, 10.9 to 15.9 in Belgium, 6.7 to 10.4 in Croatia, 9.0 to 18.3 in Hungary, 11.4 to 19.0 in Luxembourg, and 7.9 to 14.6 in Slovenia, in the periods 1989–1993 and 2004–2008 [14]. In The Netherlands, the incidence rate per 100,000 children between 0 and 14 years of age increased from 11.11 to 21.4, between 1980 and 2010; and in Germany, from 19.4 to 22.9, in the periods 1999–2003 and 2004–2008 [15,16]. In the UK, the incidence rate per 100,000 children between

0 and 15 years of age increased from 17.7 to 28.2, in the periods 1989–1993 and 2004–2008 [14].

### Pancreas transplantation rates

In the past 20 years, a total of 24,484 pancreas transplantations were performed in the USA, while 4656 transplants were performed in the Eurotransplant region, and 2537 in the UK. In Fig. 2, we show the yearly number of pancreas transplantations; and in Fig. 3, the transplant rates per million inhabitants. In the USA and the Eurotransplant region, the transplant numbers show a shift from growth to decline in 2004, with the highest annual transplant number of 1484 in the USA (5.1 per million inhabitants) and 282 in the Eurotransplant region (2.4 per million inhabitants) (Table 1). The average annual growth in the number of pancreas transplants, until 2004, was 4.1% in the USA and 1.7% in the Eurotransplant region. Concurrently, the average annual growth rate per million inhabitants, was 2.9% in the USA and 1.5% in the Eurotransplant region, corresponding with a linear fitted slope of  $0.13x + 4.1$  and  $0.04x + 2.1$ , respectively. The average annual decline in pancreas transplantation, from the year 2004–2016, was 2.9% in the USA and 1.8% in the Eurotransplant region. Concurrently, the average annual decline rates per million inhabitants, was 3.3% in the USA and 2.5% in the Eurotransplant region, corresponding with a linear fitted slope of  $-0.19x + 5.2$  and  $-0.6x + 2.1$ , respectively. In the UK, transplant numbers show a growth until 2009, with 225 annual transplants (3.6 per million inhabitants), after which the total transplant numbers stabilized (annual decline of 0.5%) and the numbers per million showed an average annual decline of 1.0%. Until 2009, the transplant numbers showed an average annual growth of 60.2% and an average annual growth rate per million inhabitants of 66.7%. For the UK, this corresponds with a linear fitted slope of  $0.25x + 0.4$ , until 2009, and of  $-0.04x + 3.1$ , from 2009.

### Bibliometric analysis of pancreas transplantation publications

A total of 1534 pancreas transplantation publications were identified between 1994 and 2016, with 578 publications issued in Q1 journals. Worldwide publication trends and trends for the USA (315 Q1 publications) and the Eurotransplant region (106 Q1 publications), were analyzed (Fig. 4 and Table 2). The total number of UK publications ( $n = 27$ ) was too low for a reliable trend analysis. Worldwide publications in Q1 journals showed an annual average increase rate of 0.1%, before 2004, and an average annual decline rate of 4.1% between 2004 and 2016. This corresponds with a linear fitted slope of  $0.04x + 32.7$ , before 2004, and of  $-1.75x + 39.8$ , after 2004. Publications from USA-based authors in Q1 journals, showed an average annual decline rate of 2.1%, before 2004, and 3.8% between 2004 and 2016 (Fig. 5), corresponding with a linear fitted slope of  $-0.52x + 21.4$  and  $-0.80x + 19.5$ , respectively. For publications from authors in the Eurotransplant region, the average annual increase rate was 20.0%, between 1997 and 2004, with an average annual decline rate of 5.4% for the period after 2004, corresponding with a linear fitted slope of  $0.71x + 3.0$  and  $-0.79x + 13.4$ , respectively.

A total of 10 original articles with >100 citations, published between 1997 and 2016, were selected. Nine out of ten publications were from USA-based authors and five out of ten used data from the UNOS database. The University of Minnesota was the institute with the most impact (5/10 highly-cited publications) in this field. Collaborations between countries were scarce, with only two joint publications, both between the University of Minnesota and the University of Padua.

In summary, a clear decline in transplant numbers in the USA,

### Diabetes prevalence

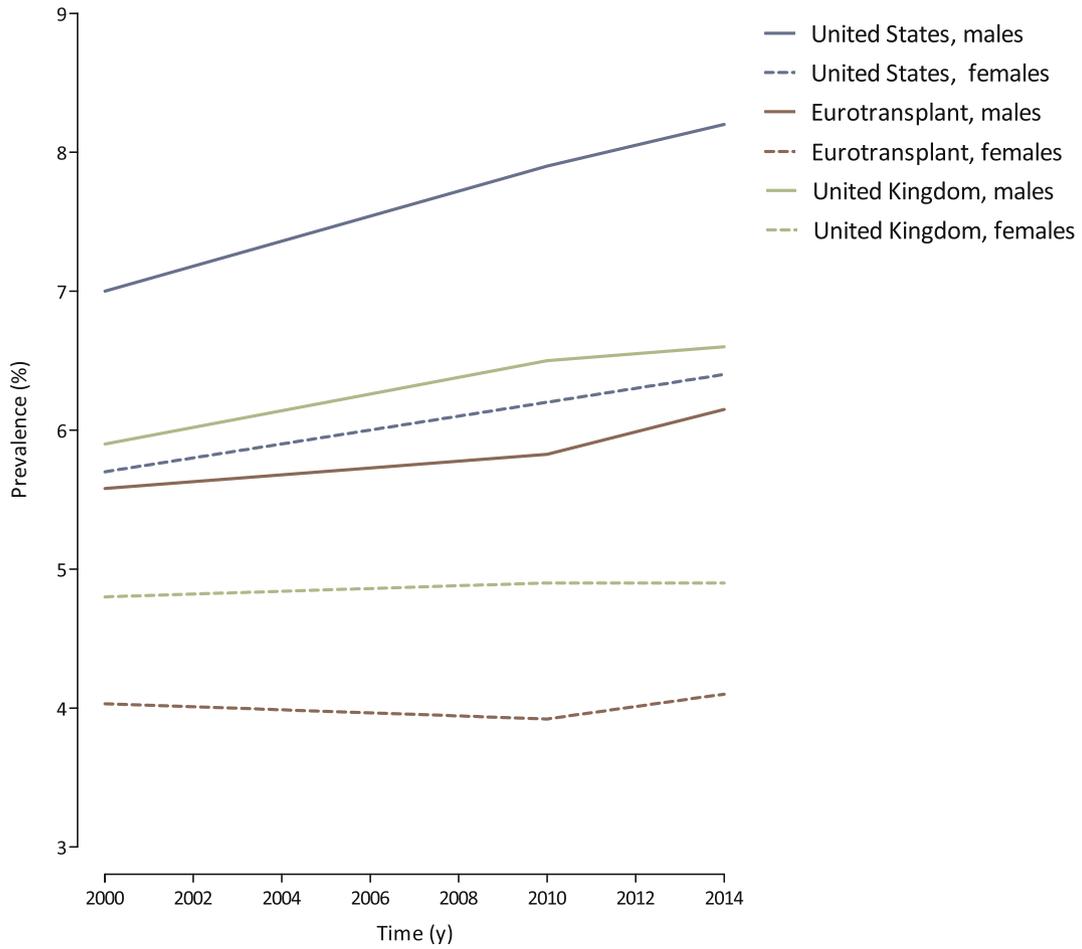


Fig. 1. Diabetes prevalence in the USA, Eurotransplant region and UK, with data at 2000, 2010 and 2014.

### Pancreas Transplantations

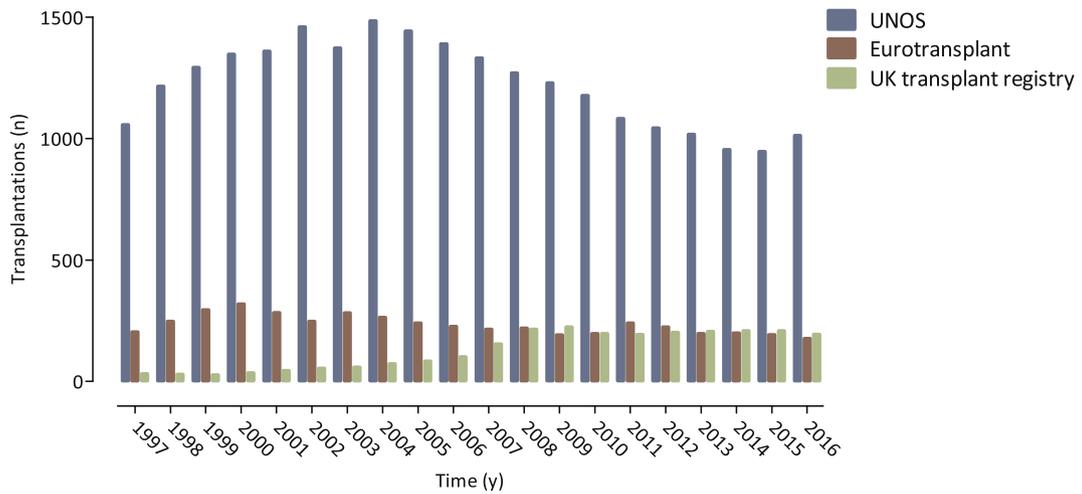


Fig. 2. Yearly number of pancreas transplantations for the past 20 years, given for UNOS, Eurotransplant, and the UK transplant registry.

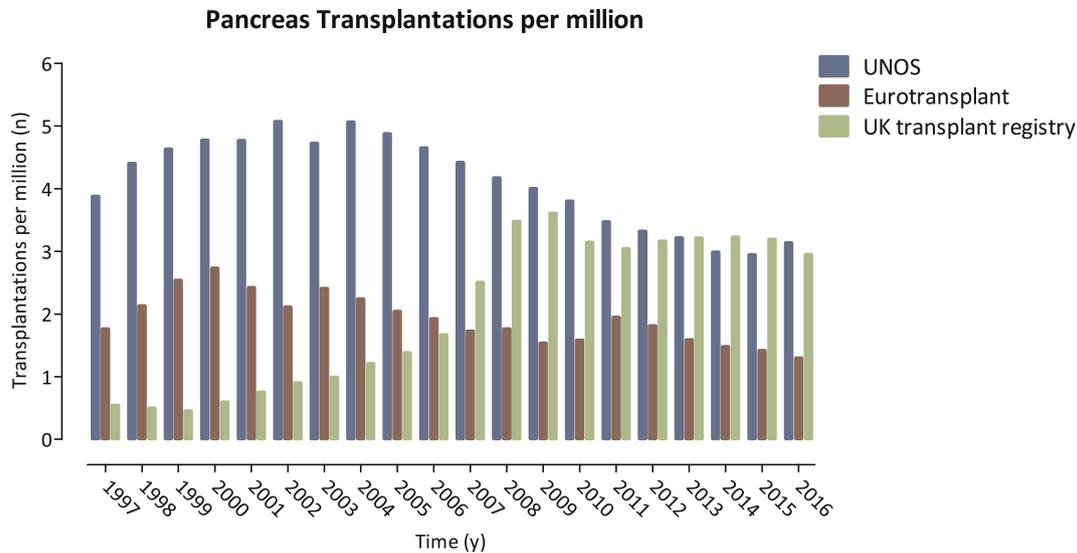


Fig. 3. Pancreas transplantation rates per million inhabitants for the past 20 years, given for UNOS, Eurotransplant, and the UK transplant registry.

Table 1  
Trend of pancreas transplantations, 1997–2016.

Region	Transplants, n			Average annual growth rate, %	Average annual decline rate, %	Transplants per million, n		Average annual growth rate, %	Average annual decline rate, %
	1997	2016	Total			1997	2016		
UNOS	1057	1013	24,484	4.1 (until 2004)	2.9 (from 2004)	3.9	3.1	2.9 (until 2004)	3.3 (from 2004)
Eurotransplant	204	177	4656	1.7 (until 2004)	1.8 (from 2004)	1.8	1.3	1.5 (until 2004)	2.5 (from 2004)
UK transplant registry	32	194	2537	60.2 (until 2009)	0.5 (from 2009)	0.5	2.9	66.7 (until 2009)	1.0 (from 2009)

UNOS = United Network for Organ Sharing, United States database.  
UK transplant registry = United Kingdom national database.

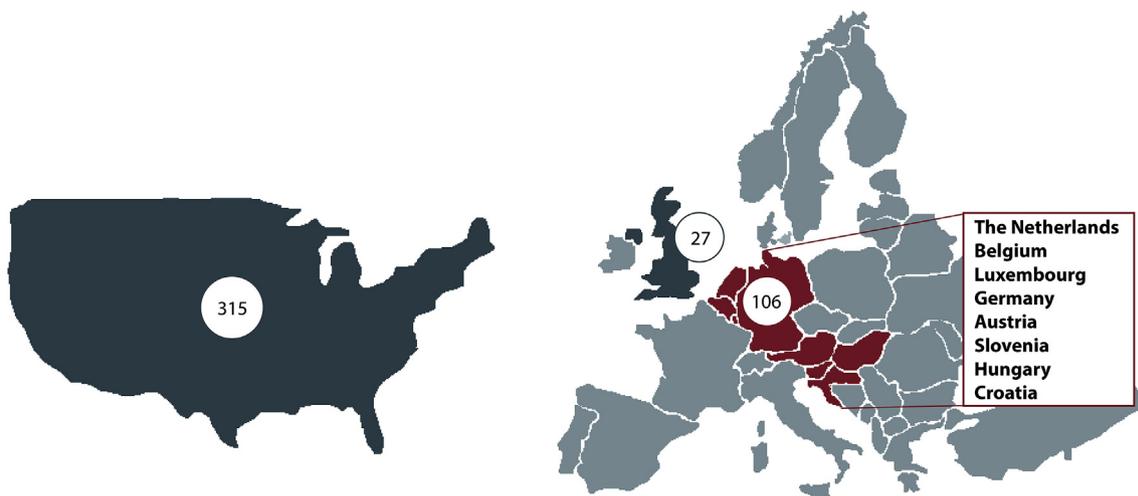


Fig. 4. Total number of scientific publications on pancreas transplantation in the USA, Eurotransplant region and UK.

Eurotransplant region and UK is evident. Following this trend, the number of scientific publications in this field is declining worldwide and specifically in the USA and Eurotransplant region.

**Discussion**

This study shows a decline in both the total and the population adjusted number of pancreas transplantations in the Eurotransplant region. In the USA, both the total and the population adjusted

the number of pancreas transplantations declined between 2004 and 2015, but a small upward trend was noticed in 2016. In the UK, the total transplant numbers stabilized after 2009, while the population adjusted number of transplantations showed the first signs of a decline. These findings are not in line with our expectations, since the prevalence of type 1 DM and C-peptide positive DM, in the male population, is still rising. Furthermore, outcomes of pancreas transplantation have improved significantly, with high patient and transplant survival rates in the USA, Eurotransplant region, and the

**Table 2**  
Trend of pancreas transplantation Q1 publications, 1997–2016.

Region	Publications, n				Average annual change rate, %	
	1997	2004	2016	Total	Until 2004	From 2004
Worldwide	34	43	17	578	+0.1	−4.1
UNOS	21	21	11	315	−2.1	−3.8
Eurotransplant	6	14	4	106	+20.0	−5.4

UNOS = United Network for Organ Sharing, United States database.

UK [24–27]. Meanwhile, we found a decrease in the number of pancreas transplantation publications, with a decline of 3.8% in the USA, 5.4% in the Eurotransplant region and 4.1% worldwide, with studies with the highest impact performed in the USA using primarily UNOS data.

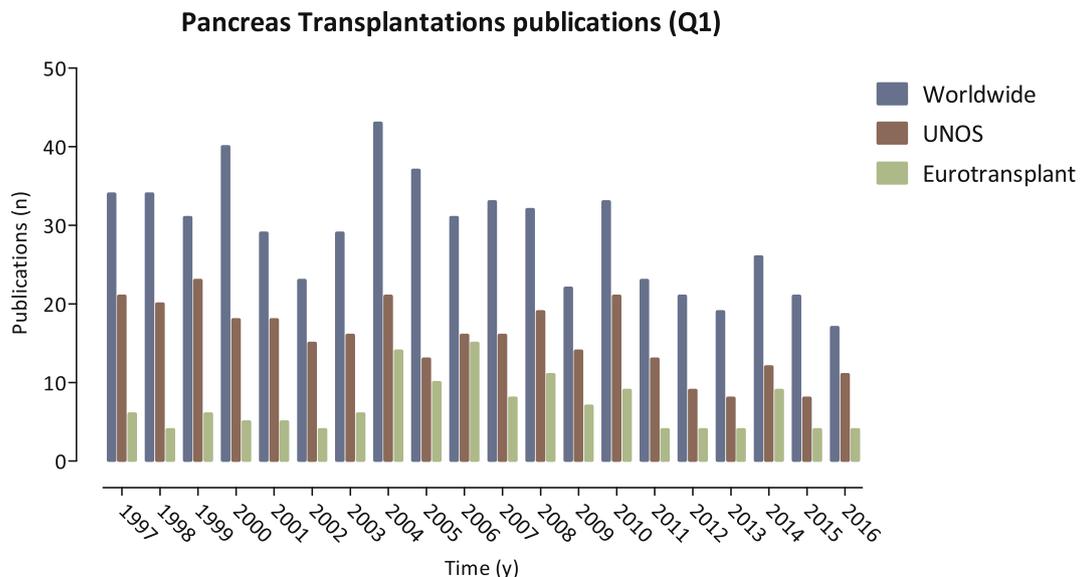
Earlier publications reported a decline in pancreas transplantations in the USA of 20%, when comparing the periods 2005–2009 and 2010–2014, with an increasing number of transplantations in non-US countries [3,4]. The most recent publication reporting on global pancreas transplantations trends confirmed the decline in pancreas transplantations in the USA, while reporting stable numbers in the UK and the Eurotransplant region. The authors reviewed the number of transplants between 2006 and 2015, without adjusting for the increasing population size in the three regions [7]. In contrast to the literature, our study shows an evident decline in transplant numbers in the Eurotransplant region and first signs of a decline in the UK.

In the past years, several publications have described the possible explanations for the decline in pancreas transplantations. Referred to as “an alarming crisis in confidence”, Stratta et al., advocated for a national initiative to “reinvigorate” pancreas transplantation as a preferred option for selected patients [6]. Multiple factors have been suggested which may be contributing to this decline. First, the ongoing academic dispute regarding the role of pancreas transplantation within the multiple treatment options available for DM may be responsible for a lack of primary referrals by nephrologists, endocrinologists and diabetologists. Second, the possible denial of the fairly good long-term outcomes after pancreas transplantation, with a patient survival of 91.8%–96.9%–100.0% at 1-year and 78.2%–89.6%–91.1% at 5-years after

transplantation, for pancreas transplantation alone (PTA), simultaneous pancreas-kidney transplantation (SPK), and pancreas after kidney transplantation (PAK), respectively [24]. Third, an underuse of donor pancreata due to a decline in experienced recovery teams. And fourth, data of the International Pancreas Transplant Registry (IPTR) shows that the current decline in the USA is predominantly due to the decline in primary and secondary PAK [3]. Partly this decline in PAK could be explained by the recent advancements in pancreatic islet transplantation, continuous glucose monitoring with insulin pump therapy, and the introduction of bio-artificial pancreata, with macro-encapsulated islets. Whether these factors alone fully explain the international decline in pancreas transplantations is uncertain, and the possibility exists that other, as-of-yet unidentified factors have influenced this trend.

The downward trend in the number of pancreas transplantation publications can be a response to the decline in transplantation rates. However, there are specific factors influencing the low number of scientific studies focusing on the use of pancreas transplantation to ensure normal glucose metabolism in patients with a high risk of DM complications. First, as in accordance with other fields of organ transplantation, large international studies are mostly funded by pharmaceutical companies. These pharmaceutical companies have shifted their focus towards improvement of continuous glucose monitoring with insulin pump therapy. Second, the majority of studies within this field have been conducted in the USA. In the past years, European research institutes have made several attempts to increase their efforts with regard to this topic but have not yet achieved the intended results. Third, in contrast to other fields of organ transplantation, there is a lack of multicenter and international collaborations, leading to a decline in high volume and high impact scientific publications.

Historically, there has been a reluctance to use donation after circulatory death (DCD) donors for pancreas transplantation. Recently, two meta-analyses described the transplant outcomes after DCD and donation after brain death (DBD) pancreas donation, and found a similar allograft and patient survival after transplantation [28,29]. With the current criteria, DCD donors are a viable and safe alternative to DBD donors. To expand the donor pool, high risk donors (pediatric, elderly or high BMI) are frequently explored and used. Although a donor age between 10 and 50 years is considered optimal, pediatric donors (age 3–17) have an



**Fig. 5.** Yearly rates of scientific publications on pancreas transplantation in the USA, Eurotransplant region and UK.

excellent graft survival compared to pancreata from donors  $\geq 18$  years [30]. Grafts from donors  $\geq 45$  years generally have a higher risk for primary non-function, but a select group of extended criteria donors organs should still be considered for patients with limited access to younger donors [31,32]. Regarding obese donors, the incidence of surgical complications in pancreas recipients has increased, but does not affect early, 1 year or 3 year graft function post-transplant [33].

A European expert group recently highlighted the challenges related to the increasing number of DCD pancreata and the need for new methods to reduce ischemia-reperfusion organ injury [34]. These experts described encouraging but limited clinical data on the use of normothermic regional perfusion (NRP) or the use of hypothermic machine preservation (HMP) after procurement. Controlled DCD procurement using abdominal NRP has been evaluated in various feasibility studies. A single simultaneous pancreas-kidney transplantation and four similar procedures in two other studies all resulted in a good initial renal and pancreas graft function [35–37]. In addition, preliminary results and experience in the field of kidney transplantation could provide guidance for the use of thrombolysis and oxygen persufflation prior to pancreas transplantation [38,39]. Recently, there has been a technological revolution in DM therapy with the introduction of continuous monitoring, sensor-augmented insulin pump therapy and closed-loop or artificial pancreas systems [40,41]. Although this has led to an improvement in target glycemic control, a physiological feedback is lacking and daily insulin requirements can vary due to complex interactions. New dual-hormone pancreas systems have been shown to be superior to single-hormone systems in preventing hypoglycemia responsive target glucose concentrations [42,43]. These developments have and will continue to exert pressure on the pancreas transplantation program, despite the differences in selection criteria and patient suitability.

In 2000, pancreatic islet transplantation was introduced as a viable treatment option for patients with type 1 DM, with the publications of the Edmonton Protocol. This resulted in a peak in allogeneic islet transplant between 2000 and 2005, followed by a lack of further improvements until 2009. Between 2009 and 2012, a second peak in islet transplant numbers was seen after broader introduction within the different European healthcare systems. In the past 6 years, the rise in islet pancreas transplant numbers has come to a halt, partly explained by the lack of reimbursement of this procedure in the USA [44]. Within the past 18 years, pancreatic islet transplantation has shown to be a promising alternative for a select group of patients with type 1 DM. Although a recent review concluded that the effectiveness is biased by very low-quality evidence, islet transplantation improves glycemic control and diabetes related complications for patients with type 1 DM when compared with prolonged insulin therapy [45]. In type 1 DM patients with kidney disease, simultaneous islet-kidney or islet-after-kidney transplantation improves glycemic control and secondary diabetic complications. When comparing pancreatic islet transplantation to whole pancreas transplantation, adverse events for simultaneous islet-kidney or islet-after-kidney transplantation were in general less severe than for whole pancreas transplantation. Long-term insulin independence and HbA1C levels  $<7\%$  remain difficult to achieve after islet transplantation [46,47]. Commercially introduced in 2000, continuous glucose monitoring with insulin pump therapy was considered a breakthrough to achieve stable glycemic control. A lack of accuracy resulted in a delayed introduction until larger studies were published between 2008 and 2010. With the introduction of monitoring systems with the necessary accuracy and precision, application was recommended by international guidelines published in 2013 [48]. In 2017, the results of the first phase 1 trial evaluation the use of bio-artificial pancreata, with

macro-encapsulated islets, were published. Studies focusing on this topic show promising results, however, broader application warrants initiation of larger clinical trials evaluating the long-term function of transplanted cells [49].

In the past 20 years, several publications have reported significant improvements in both patient and transplant survival [24–27]. A significant difference was seen in early pancreas transplant survival between simultaneous kidney pancreas transplant (91%), pancreas transplant alone (85%), and pancreas after kidney transplant (77%), in the UK [27]. Furthermore, reports show a higher patient survival for recipients with type 1 DM compared to patients with C-peptide positive DM, with a higher recipient age and higher comorbidity rate in the second group [24]. Increasingly, patients with C-peptide positive DM are considered good candidates for pancreas transplantation. And although a controversial choice in many programs, in selected C-peptide positive DM patients, SPK outcomes are very good with complete restoration of euglycemia and freedom from insulin dependence and dialysis [50]. Unfortunately, cardiovascular complications and mortality during follow-up led to a high mortality rate in patients with functioning grafts. It could be the role of International guidelines to create awareness for the need to select the appropriate C-peptide positive DM patients for PTA or SPK transplantation, so as to avoid these adverse outcomes.

Looking at achieving further improvements, focus should be placed on the disparities between groups of recipients and the addressed risk factors, such as higher donor/recipient age, higher donor/recipient BMI, and re-transplantation [25,26]. Center-related factors, such as the effect of center-volume and recovery team experience on pancreas transplantation outcomes, should be more extensively studied to compile clear healthcare policy recommendations [25]. In light of these pending research questions, the establishment of collaborations between centers and an international registry seems essential. A collaborative approach to sharing registry data can help support and enhance the impact of the academic work in this field, and avoid the duplication of research efforts.

During the past 20 years, collaborations such as the Pancreas Investigators Vital Outcomes Trial (PIVOT) Study Group, the Euro-SPK Study Group, IPTR and the UNOS database have been established. To date, only the UNOS database has managed to sustain data collection for a long time period, resulting in scientific research and findings with high clinical impact, while the PIVOT and Euro-SPK study groups have ceased operations. The improving outcomes of pancreas transplantation can only be valued when compared to other types of DM therapies in large multicenter studies. Currently, the survival benefit of pancreas transplantation compared to insulin therapy for type 1 DM is based on two large retrospective UNOS database studies. Results of international collaborations are lacking [51,52]. Furthermore, there is currently no evidence for the use of pancreas transplantation as a routine treatment for patients with uncontrolled C-peptide positive DM. This further highlights the need of prospective studies to provide selection criteria for eligible patients.

## Conclusion

Adjusting pancreas transplantation rates for changes in population size showed a clear decline in transplant numbers in both the USA and Eurotransplant region, with first signs of a decline in the UK. Whereas the prevalence of DM has increased and pancreas transplant outcomes have improved, the number of scientific publications has declined worldwide, and in the USA and Eurotransplant region in particular. In order to further improve the allocation, transplantation and long-term outcomes of pancreas

transplantation, research efforts should go to multicenter and international collaborations. These collaborations would be the first step towards elaborating clear guidelines concerning patient referral, waitlist inclusion, waitlist management, donor selection, and post-transplant management. To this end, the establishment of effective collaborations between centers and an international registry may significantly improve transplant outcomes for patients with identified risk factors globally. In light of the impact the UNOS database has had since its establishment, we put forward the suggestion for a renewed European pancreas collaboration: its goal being to perform large long-term survival studies, with a focus on comparing intensive insulin therapy and islet transplantation for both type 1 DM and C-peptide positive DM.

### Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose.

### Ethics statement

This study did not involve human participants and did not require approval of an ethics committee.

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