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SHORT COMMUNICATION

Economic Burden of Chronic Pancreatitis and Implications of Total Pancreatectomy and Autologous Islet Cell Transplantation

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ABSTRACT

Context Heterotopic pancreas is usually an incidental finding during pathologic evaluation of gastrointestinal polyps or lesions encountered during endoscopy for nonspecific symptoms or unrelated conditions. However, the same neoplastic processes that occur in normal pancreas also can occur in pancreatic heterotopias. **Case report** We report two cases of intraductal papillary mucinous neoplasms arising in pancreatic heterotopia within the duodenum of two patients. These cases are among the first reports of neoplasia occurring in pancreatic heterotopia of the duodenum. Both patients are being managed expectantly, as there is currently no consensus regarding the proper follow up in these cases, particularly those that have been incompletely excised. **Conclusion** These cases highlight the potential for neoplasia in pancreatic heterotopia and emphasize the importance of careful evaluation of these lesions. Close clinical follow up and possible excision may be warranted in patients with concerning pathologic or clinical findings.

Introduction

Intractable abdominal pain due to chronic pancreatitis is managed medically in the majority of patients. A significant proportion (5-10%) of referrals to specialist pancreatic units experience such a poor quality of life that a surgical procedure is required. A number of surgical approaches are possible depending on the specific abnormality of the gland; including bypass procedures, duct decompression/ drainage and resection (either partial or total). For some patients a total (or near total) pancreatectomy (TP) is required to achieve adequate pain relief.

Combining total pancreatectomy (TP) with an islet autotransplant (IAT) avoids the inevitability of brittle diabetes. The technique can occasionally produce insulin independence for very prolonged periods; up to 20 years following total pancreatectomy [1-3]. In cases where the operation is performed at an earlier stage, islet yields are considerably higher and insulin independence rates of up to 70% are reported from the International Registry Data [1, 2, 4, 5]. Late referral for TP/IAT has a number of important consequences. In addition to the continuing loss of islet cell mass due to the ongoing inflammatory process in the pancreas, malnutrition and increasing narcotic dependence can also directly influence long term success rates after surgical resection [1]. Previous drainage or resection surgery complicates subsequent surgery due to adhesions, increases the potential for infection and can significantly reduce the islet yield.

It has been previously shown that TP/IAT results in a reduced opiate use, decreased frequency of hospital admissions for pain and improvement in quality of life [6] and this improvement can be delivered (at the very least) at a cost-neutral level for patients with chronic pancreatitis (CP) [7]. However, the cost effectiveness of TP/IAT when compared to the socioeconomic burden of CP to the health economy has not been formally examined until now. Clearly, not all patients with CP will be appropriate for such a radical intervention, hence any comparison would only apply to the small number for whom surgery would be considered.

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METHODS

There are a number of possible approaches to assessing the impact of TP/IAT and comparing it to medical management or TP alone. It is important to take into account the following when considering the impact including; the incidence and prevalence and the resultant social impact together with the reduction of that impact following treatment. Parameters which required assessing include primary care costs; hospital admission data; pancreatic insufficiency;

diabetes; pain management; surgical intervention and complications; impact on the economy due to absenteeism, early retirement and other indirect costs. Estimates of the cost of chronic pancreatitis must consider the direct and indirect impact. Although little data exists, the direct costs are more easily identified and can be assessed either by comparison with other chronic diseases (diabetes, chronic pain), study of patient cohorts or calculated arithmetically from an overall cost; when incidence and prevalence are known for the condition.

Indirect costs are much more difficult to quantify with any degree of accuracy and the issue is confounded when trying to subsequently assess objectively the impact of a proposed treatment. Nevertheless approaches do exist for chronic diseases and in the last decade a number of groups have attempted to identify the real economic burden of a number of these conditions and the approaches are applicable to patients with chronic pancreatitis. To estimate the direct and indirect costs, local data from patients treated in Leicester has been used; in addition to a Medline literature search using keywords 'chronic pancreatitis', 'economics', 'social', 'costs', 'diabetes', 'chronic pancreatitis and chronic pain' and 'incidence'. For the Medline search the inclusion criteria were studies examining any aspect of socio-economic costs in chronic pancreatitis. Search limits were English language manuscripts only. All articles retrieved had the references crosschecked to ensure capture of cited pertinent articles.

By combining these two approaches we have been able to estimate the total socio-economic costs of chronic pancreatitis, both direct and indirect, and exhaustively gather all available data on incidence, rates of hospital admission, costs of treating chronic pain, numbers requiring intervention and numbers developing exocrine and endocrine deficiency with the associated costs.

RESULTS

Incidence and Prevalence of Chronic Pancreatitis

There remains a paucity of data concerning the incidence of CP, particularly studies investigating changes in disease frequency over time. There is one exhaustive study of the French population with estimated incidence rates of 7.7 per 100,000 and prevalence estimated at 26.4 per 100,000 [8]. Although clear data is not available for the incidence in the UK, the prevalence has been previously estimated at between 40 and 70 per 100 000 [9]. However, in a recent study Jupp *et al.* collated epidemiological data from 14 studies which suggested that the incidence of CP in Europe is 6-7 per 100 000 and the prevalence is 13-70 per 100 000 [10]. Globally, the incidence of CP ranges from 1.6 to 23 cases per 100 000 per year and the prevalence of CP is about 50/100,000 persons [11, 12] There also appears to have been a gradual increase in some countries including the UK (demonstrated by greater numbers of hospital admissions for acute and chronic pancreatitis) [10, 13, 14]. Increases in the prevalence of CP could result from greater availability of high-quality cross-sectional imaging techniques that can detect morphologic changes in the pancreas. Alcohol consumption has been increasing in developing countries, such as China and India (Global Status Report on Alcohol and Health 2011) [15] due to rapid urbanization and increased affluence. This increase would be expected to increase the burden of alcohol-related pancreatitis in these countries. In contrast, alcohol consumption has been generally stable or decreased in many North American and European countries although studies from the USA and Japan have also noted increases in incidence of the disease [11, 16, 17].

Dite and colleagues also stated that the median time from the onset of the first subjective symptoms attributable to chronic pancreatitis to diagnosis was a median 3.2 years (range 1-5 years) [18]. Mortality from CP is initially low but as the disease progresses mortality steadily increases and is related to duration. The 5, 10 and 20 year survival is 97%, 70-86.3% and 45-63% respectively [10, 18]. These increases may, however, reflect a time lag prior to the reduction in alcohol intake becoming effective through a lower incidence of benign disease particularly acute pancreatitis [11].

Hospital Admissions Due to Pain from Chronic Pancreatitis

The most frequent symptom of CP is pain which may manifest as an acute exacerbation or as constant disabling pain [19]. Pain is the most common cause of hospital admissions often necessitating interventional procedures and despite extensive research the treatment of CP remains mainly empirical. In addition to pain, exocrine insufficiency, pancreatogenic diabetes, local pancreatic complications and psychosocial issues associated with the disease are additional therapeutic challenges placing a significant burden on healthcare systems. The protracted and variable course of chronic pancreatitis makes quantifying direct and indirect costs difficult and the economic burden of CP is poorly defined in the literature. Although a number of studies have demonstrated poor quality of life in patients with CP [20-22], few have examined the indirect costs of this to society. Undoubtedly however, chronic pancreatitis imposes a large, but difficult to quantify, burden on health care systems, particularly in developed countries. In the USA, benign pancreatic diseases including chronic pancreatitis require 327,000 admissions to hospital each year, generating 200,000 attendances at emergency departments and 532,000 visits from doctors [23]. The overall cost in the year 2000 was $2.5 billion [24, 25].

Pain represents the most common and difficult to control feature of CP, resulting in an inordinate degree of disability and which alone in the USA has been estimated to cost in excess of $638 million per annum [26]. Although similar data does not exist for the UK, Hospital Episode Statistics for 2009/2010 show that there were in excess of 12,000 UK admissions coded as "chronic pancreatic disease", most as emergencies with a mean length of stay of 6.2 days (HES 2009/2010) [27]. This data probably underestimates the true scale of the problem but even based on these figures

and estimating the cost (based on a single day of emergency care and 5.2 days of prolonged ward care) would equate to the National Health Service (NHS) spending of £55.8 million annually. This cost is simply for emergency admissions due to symptoms/complications of CP and does not account for the care in the community, outpatient visits, 700 surgical procedures carried out on CP patients each year, social problems related to unemployment and the burden related to unrecognized cases (National Health Service: Hospital Episode Statistics 2011) [27]. A further measure which is also difficult to quantify but nevertheless has to be considered, is the delay in discharge because of the need for social packages to help support these patients in the community after discharge. The loss in elective activity generated by these admissions is also discounted from these figures.

Five articles were identified examining the numbers of CP discharges per year. Jaakkola *et al.* found that in a Finnish population the incidence of CP discharges increased between 1977 and 1989 from 10.4 to 13.4/100,000/year based [28]. In England and Wales between 1962 and 1974 an increasing incidence of discharges in CP of between 7-32.4/1,000,000/year has also been demonstrated [29]. This change correlated with an increase in alcohol consumption per capita. Yang *et al.* examined epidemiological data for alcohol related disease in the USA between 1988 and 2004 and found the mean incidence of discharges to be 8.1 (CI 7.7-8.6) per 100 000/year [30]. They observed no change in rates of discharges over the 17-year study period.

Unfortunately data from the UK is lacking. Hospital Episode Statistics for 2009/2010 show that there were in excess of 12,000 UK admissions coded as "chronic pancreatic disease", most as emergencies with a mean length of stay of 6.2 days [27]. From this data a probable underestimate of cost (based on a single day of emergency care and 5.2 days of prolonged ward care) would equate to an NHS spending of £55.8 million.

Mullady and colleagues examined the number of CP sufferers in the USA who were admitted with pain [31]. Of the 414 patients studied over 90% of them were hospitalised on at least one occasion in their lifetime for pain attributable to CP. Patients with constant pain were more likely to have been hospitalized (frequently more than 10 times in the preceding year) than those with intermittent pain. Similarly, patients with intermittent pain were more likely to have had less than 2 hospitalizations over their entire lifetime for pain related to their CP while those with constant pain patterns were more likely to have more than 10 hospitalizations.

Loss of Revenue from Chronic Pancreatitis Pain and Associated Diabetes

Chronic pain is associated with the poorest indices of quality of life. It is associated with absenteeism, reduced productivity and a high risk of leaving the labour market [32]. These indirect costs are difficult to quantify in the case of CP but there can be little doubt that they will be substantial. Estimates of the direct costs of pain in CP in the USA are around $638 million annually but this clearly reflects an underestimate of indirect costs. In Sweden in 2003 the loss of production secondary to sick leave from chronic pain constituted 91% of the socio-economic cost at Swedish Krona 87.5 billion (9.2 billion Euros) [32]. Similarly, in Denmark, an estimated 1 million working days are lost annually secondary to chronic pain. The percentage of this cost attributable to CP is unknown [33].

The study by Wehler *et al.* looked at 265 patients with CP [20]. They found that 14% of patients took disease related early retirement and 13% had a period of prolonged unemployment. Forty percent had disease related absence from work in the preceding 12 months. In 17% of these, this was for up to a month in duration. There is no data to our knowledge of indirect costs attributable to CP from this lost productivity. Data from the USA of costs secondary to lost production from work related absenteeism, reduced productivity, unemployment and premature mortality from all cause diabetes is $58 billion per year (Economic Costs of Diabetes in the U.S. in 2007) [34, 35]. If we assume that PD accounts for 0.5-1% of all diabetes, then indirect costs could be as high as $29-58 million from diabetes alone in CP. Again, the brittle nature of PD probably underestimates this and it does not take into account indirect costs due to chronic pain.

Costs from Pancreatic Endocrine and Exocrine Insufficiency

Pancreatic endocrine insufficiency secondary to destruction of acinar cells is an inevitable complication of chronic pancreatitis. Depending on etiology and duration pancreatogenic diabetes (PD) develops in 40-60% of patients with CP [36]. Its rates are highest in alcoholic and tropical CP. At 10 and 25 years from diagnosis, 50% and 83% of patients respectively develop this complication. The complications of PD are similar to type II diabetics except that coronary artery disease is less common in PD [36]. The rates of developing retinopathy, nephropathy, neuropathy and peripheral vascular disease are however similar. Glycaemic control is often difficult to achieve due to its brittle nature and the high frequency of hypoglycaemia. In patients with PD the median survival is 25 years after diagnosis. Mortality is frequently secondary to nephropathy [37].

In the NHS, diabetes and its related complications costs 10% of the total budget equating to around £9 billion per year (Prescribing for Diabetes in England: 2004/5 to 2009/10, Diabetes in the UK: Key statistics on diabetes 2010)[38]. PD accounts for 0.5 to 1% of all diabetes and therefore costs can be estimated at around £45-90 million per year. Its brittle nature means that this figure may underestimate the true cost of diabetes from pancreatic insufficiency. In 2006, prescription costs for all causes of diabetes were £561.4 million. Extrapolating this for PD, the prescription costs are estimated at around £2.8 to 5.6 million a year. In addition, patients with all-cause diabetes experience prolonged hospital stays compared to non-

diabetics at a cost of 80,000 bed days per year. Assuming that PD accounts for 0.5-1% of all diabetes this accounts for 400 – 800 bed days per year. Calculations based on a bed day cost of £225 (www.institute.nhs.uk), equates to £90,000 to 180,000 in prolonged stay costs. Fifty seven percent of patients with CP take enzyme supplements [10]. In the USA costs for all prescriptions in pancreatitis were estimated at $88.6 million in 2004 [26]. Pancreatic exocrine enzyme replacement constituted 84.8% of these costs equating to $75.1 million a year.

Costs from Surgical Intervention in Chronic Pancreatitis

It is estimated that 50% of patients with CP will require surgical intervention for the treatment of pain or for the management of complications [20]. In total, approximately 700 surgical operations are carried out in the UK per year for CP and its related complications (Hospital Episode Statistics) [27]. These range from bypass, drainage and resectional procedures to total pancreatectomy. To our knowledge no direct data exists for the costs of these procedures and the figure is likely to represent a significant underestimation.

Other Direct and Indirect Costs from Chronic Pancreatitis

Estimates of direct and indirect costs as a result of CP can be calculated from the available data and the figures from the USA are particularly helpful due to the accurate figures provided by insurance companies **(Table 1)**. The estimated total per annum cost in the USA is $3.57 billion (£2.177 billion). With the assumption of a CP prevalence in the UK of 13 to 26.4 per 100,000, based on the UK population of 63.9 million there will be 9,841 to 16,870 patients with CP in any one year and the total annual cost will be £454 million. This equates to a cost/annum/person of £26,912 to 46,133.

Having an approximation of the total costs means that it is possible to estimate the indirect component if the direct costs are available. It is important to remember that Health care costs in the USA are probably somewhat higher than in the UK however, this is probably offset when considering the patient cohort suitable for TP/IAT, since only very severely affected individuals are considered for treatment **(Figure 1)**.

Cost α prevalence

$$C^{total} = n \times Individual^{total\ c}$$

$$(Direct + Indirect)^{total\ c} = n \times (Direct = Indirect)^{ind\ c}$$

n =population/prevalence

There are clearly major difficulties in determining the true impact of chronic pancreatitis on the healthcare system although direct costs are easier to assess than indirect. Examining data which can be reliably assessed from hospital episode statistics of clinical notes, for example recording of hospital admissions before TP, is likely to be an under-estimate in both frequency and length of stay. However, following surgery readmissions are more accurately recorded as this would then coincide with the patient entering a prospective database (which most highly specialised units offering TP/IAT will have). This problem also relates to the analgesia records and intervention costs before and after surgery. However this imbalance will serve to underestimate the treatment costs without surgery and therefore makes the considerable financial saving with TP, even more significant. Community costs and out-patient surveillance costs are not easily quantifiable and have been excluded from the analysis. The long study period (up to 20 years) required is another confounding factor in this

Table 1. Socio-economic costs of chronic pancreatitis - Calculations are based on an assumption of an exchange rate of £1=US $1.64, the population of USA at 4.97 times that of the UK and taking the UK prevalence of chronic pancreatitis as 15.4-26.4/100 000 from the recent study by Jupp *et al.* rather than the previous higher estimate of 40-70/100 000 by Mitchell *et al.*

	United States	United Kingdom
Incidence/100 000	5-12	6-7
Prevalence/100 000	50	15.4 – 26.4
Population 2000	281.4 million	58.7 million
Population 2014	317.3 million	63.9
Affected individuals	158 650	9 841 – 16 870
Admission rate/year	327 000	?
Pain	$638 million	?
Total cost 2000	$2.5 billion	-
Total cost 2014**	$3.57 billion (£2.177 billion)	£454 million
Individual cost/year	$22 502	£26 912 - 46 133

**Inflation 2000 to 2014 - 42.66%

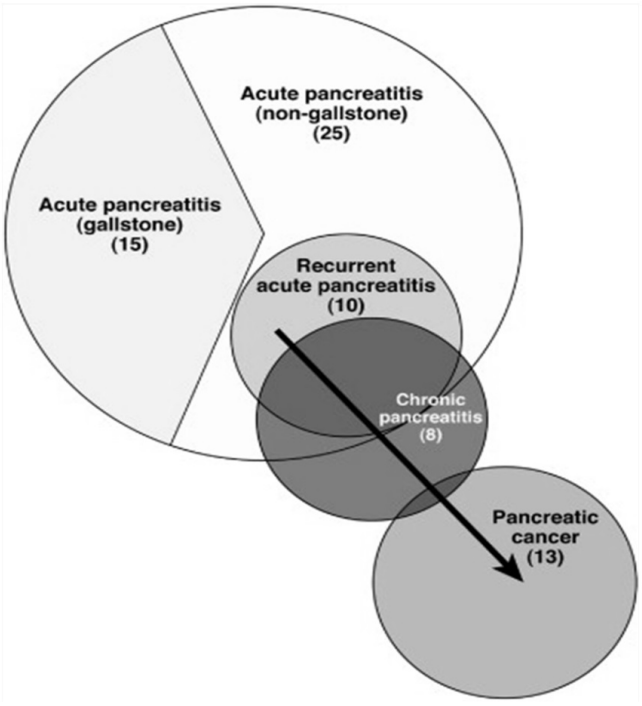

Figure 1. Incidence rates for pancreatitis and pancreatic cancer in the United States. Numbers in parentheses indicate approximate yearly incidence rates per 100,000 persons. The arrow indicates the relationship between benign and malignant disease. Recurrent AP develops predominantly in patients with non–gallstone-related pancreatitis, although it can develop in patients with gallstone-related pancreatitis when cholecystectomy has been delayed or refused (from Yadav and Lowenfels 2013).

assessment, as many costs will have significantly changed over that period.

The exclusion of insulin therapy from any cost-analysis is probably justified. It has been reported that diabetes is present in up 50 to 75% of patients at presentation and longitudinal cohort data suggests that up to 50% of patients develop diabetes after 20 years from diagnosis It could be reasonably expected that up 80% of patients would have developed diabetes during the follow-up period of this study (incorporating the 5 years pre-TP interval and the 16 year median survival post-operatively) [7]. This is a relatively conservative estimate and the true incidence could, in reality, be higher. Insulin therapy varies enormously, but for the purposes of cost comparison, absolute values matter little. With a set price of £20 per 1000 units of insulin (loosely based on British National Formulary (BNF) data over a range of preparations) the price per unit of insulin is 2 pence for each insulin unit. Patients would likely to be poorly-controlled diabetics and hence their insulin requirements would be similar to TP patients without islet cell transplantation (35 IU per day) [7], this would amount to an annual insulin therapy cost of £178.80 in the 80% of patients becoming insulin dependent. Insulin therapy costs for patients undergoing TP with islets (with daily requirements of 22 IU per day) are £160.60 annually.

Efficacy of Total Pancreatectomy and Islet Cell Transplantation

There is no specific evidence addressing the cost effectiveness of pancreatectomy and islet auto transplantation compared with pancreatectomy alone but this can be estimated by extrapolating from studies relating to islet cell transplantation. There are significant risks to doing this since success rates and long-term graft function are not directly comparable. However, as a crude model to assess if islet transplantation is cost-effective when compared to standard management of diabetes (either acquired or surgically induced) there is some merit to this approach. Beckwith and colleagues recently analysed the cost-effectiveness of islet cell transplantation compared to standard insulin therapy in Type 1 diabetes in the United States, using estimates from the literature and clinical trial costs [25]. They found that for insulin therapy, the cumulative cost per patient during a 20 year follow up period, was $663,000 and cumulative effectiveness was 9.3 quality-adjusted life years (QALY); giving an average cost-effectiveness ratio of $71,000 per QALY. Islet cell transplantation was more cost effective than standard insulin treatment having a cumulative cost of $519,000, a cumulative effectiveness of 10.9 QALY and an average cost effectiveness ratio of $47,800 per QALY. They also found that islet cell transplantation was cost saving in long run, and cost effective in the short-term compared to insulin treatment. Unlike cell transplantation, IAT is not influenced by donor factors and is free of any costs relating to immunosuppression which should further enhance its cost effectiveness. Moreover, Sutherland and colleagues have demonstrated that islet function is significantly more resilient in autografts than allografts, which would prolong the early advantage compared to insulin therapy both in terms of cost and quality of life [2]. It is likely that increased confidence in TP and IAT will see an expansion of the indications with the inclusion of patients with any benign disease undergoing a partial or total pancreatectomy.

Efficacy of Total Pancreatectomy for Chronic Pancreatitis

Although conservative medical management can sometimes alleviate mild to moderate pain associated with CP, due to the progressive nature of the disease it is estimated that greater than 50% of patients will eventually require operative intervention for severe pain [38]. A number of surgical approaches are possible depending on the specific abnormality of the gland including bypass procedures, duct decompression/drainage and resection (either partial or total) **(Figure 2)**. It is not the purpose of this review to extensively review the various surgical treatments for chronic pancreatitis, which has been done elsewhere [39], but to focus on TP and its cost-effectiveness for CP. This does, however, raise the potential of bias in that not all patients with CP are best managed by TP/IAT or indeed any type of surgical intervention. In particular, the subset of patients with alcohol-induced chronic pancreatitis are difficult to manage due to a number of issues such as poor compliance, concurrent co-morbidities and narcotic dependence. Extrapolation of cost implications in this review assumes, to some extent, that all patients with CP could be potential candidates for radical surgery (such as TP/IAT) when this is clearly not the case in reality. The proportion of patients with CP who would be suitable for any type of radical surgery is small.

Outcome of Total Pancreatectomy and Islet Autotransplantation (TP/IAT)

The world's first total pancreatectomy and islet autotransplantation (IAT) was performed at the University of Minnesota by David Sutherland in 1977 [40]. A female patient with CP had an IAT after a total pancreatectomy and subsequently remained insulin independent and pain free until her death 6 years later from a cause unrelated to her procedure [41]. Unfortunately, early attempts at islet isolation were hindered by the lack of standardized collagenase preparations (an essential pre-requisite), equipment and suitable laboratories. The development of Liberase™ in 1995 (Roche Applied Science, Penzberg, Germany) heralded the era of increasing standardization and there was a concomitant development of specialized islet isolation procedures and facilities [42, 43]. These techniques were principally developed for islet allografting but have been adopted and modified to facilitate islet autotransplantation. The number of centres able to perform IAT following total pancreatectomy has increased during the last decade and although there are to date only 20 large series worldwide, there are a significant number of additional units starting to perform the procedure as experience with islet allografting have grown.

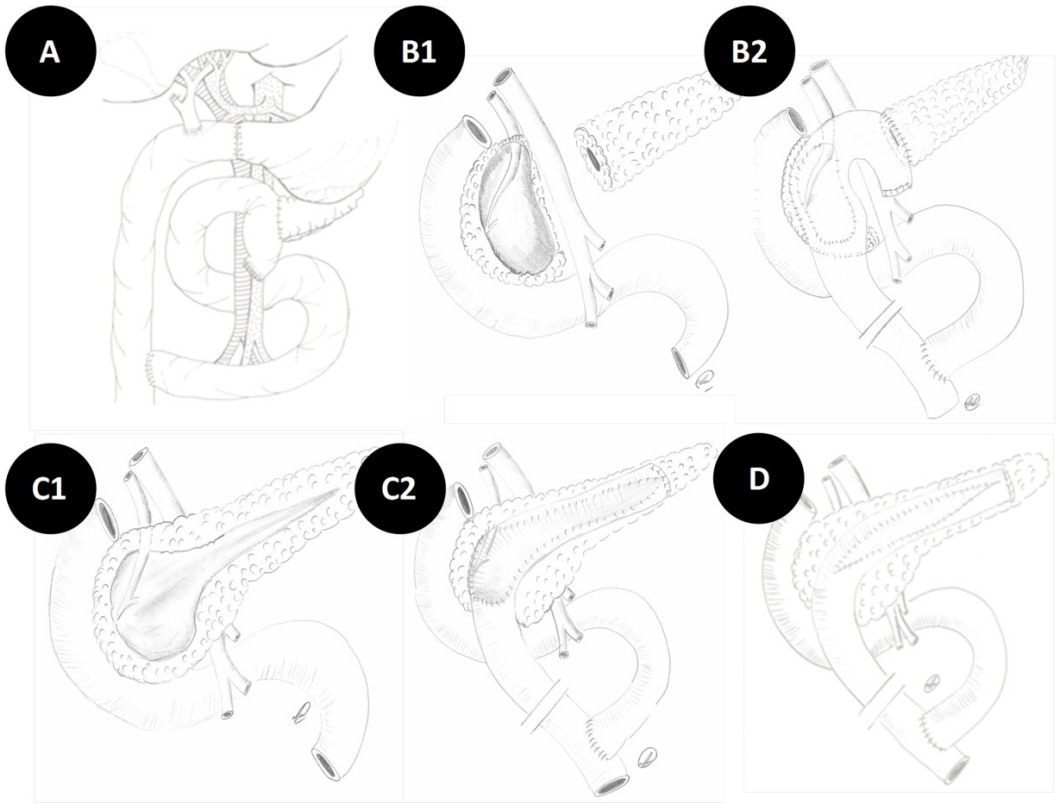

Figure 2. A selection of accepted surgical therapies for CP. **(a.).** Pylorus preserving pancreaticoduodenectomy, (b1). Duodenal-sparing head resection, **(b2.).** Duodenal sparing head resection with reconstruction, **(c1.).** Frey resection, **(c2.).** Frey reconstruction, **(d.).** Partington-Rochelle drainage procedure.

The ability of islet autotransplantation to decrease the diabetes mellitus (DM) related morbidity after extensive pancreatic resection for CP, is now well established. Islet autotransplantation can potentially result in insulin independence after a pancreatic resection and although the majority of patients do require some exogenous insulin, they will still have the benefits of long-term endogenous insulin secretion. It is the demonstration of long-term insulin production in the IAT patients, together with the known natural history of CP (which frequently leads to total exocrine and endocrine insufficiency) that has led to suggestions that TP and IAT should be considered at an earlier stage [44]. It is increasingly used as the treatment of choice to prevent long-term chronic pain, narcotic addiction, surgically induced diabetes and the deterioration of quality of life. Importantly, early resection of the pancreas has been shown to be associated with superior islet recovery, improving the chance of insulin independence following islet autotransplantation [45].

Cost-Effectiveness assessed by Examination of the Leicester Series

Costs were calculated using available data from number of hospital admissions, analgesia requirements and surgical costs from interventions before and after total pancreatectomy **(Figure 3)** [7]. All costings were derived using median values per individual patient over a one year period. Due to variance in available data prior to TP (5 years) compared to the detailed follow-up following pancreatectomy (16 years), all pre-surgery costs were extrapolated to encompass the median expected survival of patients post-operatively which was 16 years [7]. Given that costs of surgery and other interventions were "one-off" procedures these were not extrapolated over the longer-surveillance period post surgery. Only patients receiving and islet autotransplant were included in this analysis as they underwent the most expensive intervention and were consequently the best test for the cost-effectiveness of total pancreatectomy. Hence, the comparison extrapolates the "running costs" of patients before their total pancreatectomy for a 16 year period, allowing comparison with the TP/IAT patients to obtain an estimate of the financial burden that would have resulted had they not undergone surgery. This was then compared to the costs of these patients in terms of admissions and analgesia after TP/IAT. Indirect costs per patient could not be identified from this clinical retrospective series

With the total cost of care estimated at £46,133 to 26,912 per patient from previous data published in the literature summarised earlier **(Table 1)** and a direct cost of £9,465 (from data available from the Leicester series) **(Figure 4)** this implies an indirect cost of £17,447 to £36,668 per patient or taking the mean value £27,058. These indirect costs could not be factored into the analysis from the clinical series of patients, but an awareness of these costs is essential when considering the financial impact of surgical intervention.

In the Leicester series, community costs and follow-up costs were assumed to be equal both before and after surgery, as were costs of diabetes. The methods used has already been previously described [7]. The analysis demonstrated that TP/IAT was cost-effective when

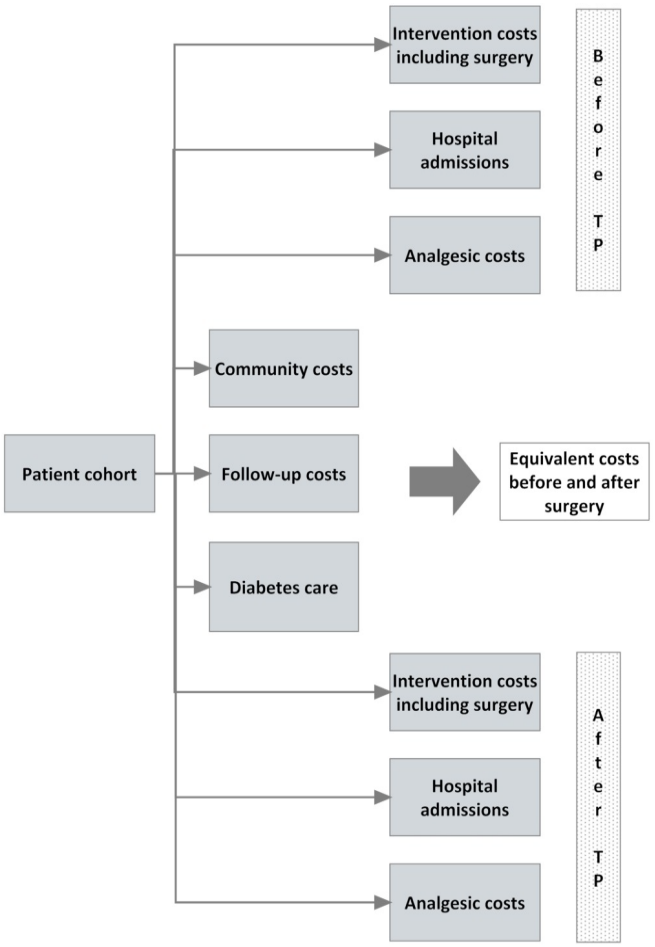

Figure 3. Method of calculating relative costs before and after TP/IAT

compared to pre-treatment costs and assumed costs for the extrapolated life-span of the patients (assuming that TP/IAT had not been undertaken) with the cost of TP/IAT being £101,608 versus £101,445 without surgery. The true benefit may be higher, however, when considering indirect costs (discussed above) such as returning to work.

Cost-Effectiveness assessed by from Other Centres

Further support regarding the cost-effective of TP/IAT can be observed from a series of 46 patients from Cincinatti [46] demonstrated that TP/IAT was associated with fewer admissions (0.9 annually) that medical therapy alone (1.6), endoscopic therapy (1.4) [46]. In addition, there was a significant reduction in opiate use, imaging requests and endoscopic interventions. Cost and survival for TP/IAT versus medical management were $153,575/14.9 QALYs and $196,042/11.5 QALYs, respectively. The same group also published data regarding the long-term efficacy of TP/IAT in reducing opiate use and stabilising glycaemic control; although some long-term deterioration in endogenous insulin production was observed over time [47]. Finally, in a more recent paper the efficacy of using TP/IAT as inital surgical treatment in the management of minimal change pancreatitis was presented (48). Once again, sustained improvements in narcotic use were obtained with 58.3% (n=49) of patients achieving narcotic independence. Significantly, postoperative insulin independence was achieved by 36.9% (n=31) of patients suggesting early definitive treatment results in a preserved islet cell mass with a greater probability of insulin independence.

DISCUSSION

Total pancreatectomy has been shown to be extremely effective in treating chronic pain and the number of admissions to hospital [6]. The addition of an islet transplant may give further benefit in terms of glycaemic control and reduce diabetic complications [49]. There is no specific evidence addressing the cost effectiveness of pancreatectomy and islet auto transplantation compared with pancreatectomy alone although this can be estimated by extrapolating from studies relating to islet allotransplantation. Beckwith *et al.* recently analysed the cost-effectiveness of islet allotransplantation compared to standard insulin therapy in type-1 diabetes [25] and found it be cost-effective.

As with all branches of transplant surgery, research and development allows progressive improvements in graft function and survival. The extensive global interest in islet allotransplantation for the treatment of diabetes mellitus means that there are a plethora of research strategies to improve islet isolation and transplantation and to prolong graft survival. Although data on international budgets spent on islet related research are not available; Diabetes UK spends an estimated £6 million per annum on islet research. Up to 41,298 peer-reviewed articles spanning 1907 to July 2011 and specifically 9039 related to islet transplantation have been published thus far. Research strategies developed for allotransplantation programmes can be directly utilized to improve rates of insulin independence following autotransplantation. Unpublished data (Leicester) suggests that the rates of insulin independence have improved with the last 8 patients transplanted (5 of 8 patients have shown periods of insulin independence) and this coincides with the introduction of the newly formulated, low endotoxin GMP grade collagenase enzyme.

In a study from Cincinnati examining the role of total pancreatectomy and islet cell autotransplantation for

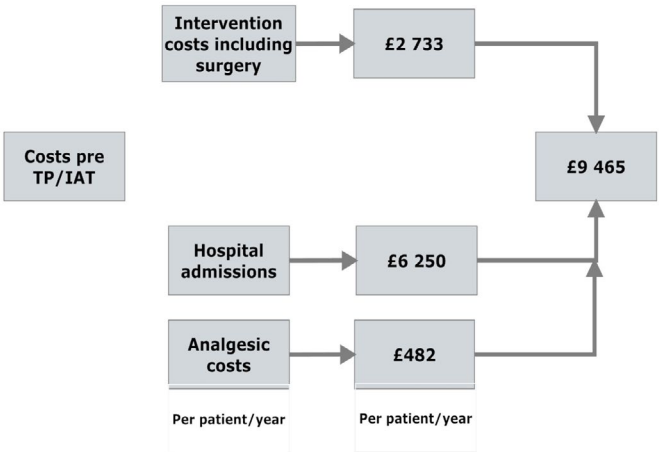

Figure 4. Pre TP/IAT costs as calculated from patients in the Leicester series prior to treatment

genetically linked pancreatitis, insulin requirements reduced to a mean of 15U/d by 22 months and 25% of patients were insulin independent. Narcotic use fell dramatically following surgery with a 63% rate of narcotic-independence (at last outpatient visit), which was also associated with a significantly improved quality of life (analysis of the 36-item short-form health survey and the McGill pain questionnaire) [50]. There are similar findings in children having a total pancreatectomy and islet autotransplant by the Minneapolis group who used the Medical Outcome Study 36-item short form (SF-36) before and after surgery and demonstrated a below average health-related quality of life pre-operatively (mean physical component summary (PCS) score of 30 and mental component summary (MCS) score of 34 (2 and 1.5 standard deviations respectively below the mean for the US population)). By 1 year following surgery the PCS and MCS scores had improved to 50 and 46 respectively (PCS $p<0.001$, MCS $p=0.06$) and mean scores had also improve for all 8 component subscales. In addition more than 60% of patients were insulin independent or required minimal insulin [2, 51].

A recent meta-analysis has also attempted to determine the reduction in morbidity and mortality conferred by the addition of and islet autotransplant to a total pancreatectomy [52]. The study found a very low 30 day mortality of between 1 and 2% (median of 0%) and insulin independence rates of 4.62 per 100-person years and 8.34% per 100-person years at last follow up and transiently respectively. Dong and colleagues did not examine the results for quality of life related to insulin independence, reduced requirements or glycaemic control but this was examined in a study from the Cleveland Clinic this year [53]. The stated aim of the study was "to improve QoL by alleviating pain and discontinuing narcotics while preventing or minimizing surgical diabetes". Patients were examined pre and post-operatively using the Depression Anxiety Stress Scale (DASS) and the Pain Disability Index (PDI). A visual analogue pain scale was used to assess global pain and diabetes was examined by the use of HbA1c. Depression and anxiety were classed as mild, moderate, severe and extremely severe and the effect on family/home responsibilities, recreation, social activity, occupation, sexual behaviour, self care and life support activities studied. Results for the impact of the surgery and islet autotransplant on those activities severely affected are shown in **Table 2**.

This 2011 study is supported by further studies demonstrating improvement in all functional scales in EORTC-C30 after TP/IAT; including general health status scored at 32.8±5.5 and 71.9±4.4 pre and post-operatively respectively. All symptom scales were ameliorated following TP/IAT, specifically pain scores but also fatigue, nausea, vomiting, anorexia and constipation (53-55). Longer term data from Rilo *et al.* from Arizona examined results from 55 patients following TP/IAT and were able to demonstrate that by 12 months post-operatively 71% were pain free and required no analgesia (56-59). The 5 year experience from the University of Virginia has also demonstrated the potential for TP/IAT to produce a significant improvement in quality of life by decreasing pain and narcotic requirements [60].

What is evident is that the lack of available data makes placing a collective monetary value of the disease difficult. The indirect cost of disease is an imprecise science and often costs are often hidden. CP, by the nature and aetiology of the disease, is refractory to treatment and the patients represent a difficult cohort due to the frequent occurrence of alcohol, tobacco and opiate co-dependencies. Frequently data from CP patients is mixed together with alcohol related disease or acute pancreatitis, making CP specific conclusions impossible. Co-morbidities (such as smoking and alcohol) are likely to contribute significantly and these are inadequately defined in the literature. Chronic pain forms a significant part of the indirect costs to society and is the sentinel symptom of CP. These chronic pain studies often fail to focus on disease specific outcomes and therefore the costs attributable to CP are unknown. Lower back pain in the UK for example had estimated indirect costs of between £5 and £10.7 billion in 1998 [59]. Chronic pancreatitis although less common, is associated with high rates of unemployment and absenteeism and will be associated significant values for indirect costs.

Another unknown direct cost is that from surgical or radiological intervention. Although there are at least 700 procedures performed every year for CP in the UK, the monetary impact of is unknown. Due to the increasing incidence of CP the financial burden to public health care systems is likely to continue to rise. Non-surgical approaches have been assessed but surgery has been demonstrated to be superior in attaining long-term pain control and improved quality of life when compared to endoscopic treatment in randomised-controlled trials [60-62]. Studies have also shown that early surgical intervention is indicated before the gland is irreversible functionally and morphologically damaged. Surgical resection continues to be the definitive treatment for severe disease and persistent pain. Previous studies have suggested that the cost of surgery can be outweighed by the reduced direct costs of the illness in terms of reduced healthcare costs, improved employment rates and improved quality of life [22, 61-69]. The findings of this review would also support this observation.

CONCLUSION

The overall healthcare burden of CP is substantial but precise costs are difficult to calculate due to the paucity of available data. Interest in the economic impact of healthcare interventions has increased dramatically in recent years and chronic conditions are known to be extremely cost. Despite CP occurring in a relatively small number of patients they consume a disproportionate volume of resources. Selective early surgical intervention

Table 2. Improvements in quality of life following total pancreatectomy and islet autotransplantation for chronic pancreatitis

	Pre-operative State	Post-operative State
Family/home responsibilities	12 (61%)	2 (10%)
Recreation	16 (80%)	4 (20%)
Social activities	13 (66%)	3 (15%)
Occupation	14 (70%)	3 (20%)
Sexual Behavior	11 (55%)	2 (10%)
Self care	6 (39%)	0 (0%)
Life support activity	9 (45%)	1 (10%)
Depression	4 (19%)	0 (0%)
Anxiety	1 (4%)	1 (4%)
Pain scale	11 (55%)	2 (10%)

can ameliorate chronic pain, preserve or improve endocrine function and reduce hospital admissions. Although quantitative data does not exist, early surgery could reduce both the indirect and direct costs of CP. A more robust method of collating data from patients with CP is required to allow meaningful cost-calculations to be made.

Conflict of interest

Authors declare to have no conflict of interest.

References

1. Bellin M, Beilman G, Dunn T, Chinnakotla S, Pruett T, Hering B, Wilhelm, Baramurugan AN, Sutherland D. Longevity of insulin independence after islet autotransplant is more common in patients with a short duration of disease. Transplantation 2013; 96:6S-26.

2. Bellin M, Beilman G, Dunn T, Chinnakotla S, Balamurugan AN, Bland B, Vickers S, Hering B, Sutherland D. Insulin independence and metabolic outcomes in a large cohort of total pancreatectomy and islet autotransplant recipients. The Review of Diabetic Studies 2011; 8: 100.

3. Pollard C, Gravante G, Illouz S, Webb MA, Chung WY, Ong SL, Dennison AR. The long-term outcome of islet autotransplantation following total pancreatectomy: the Leicester experience. The Review of Diabetic Studies 2011; 8: 100.

4. Wilson CH, White SA. Single-centre experience of laparoscopic pancreatic surgery. Br J Surg 2010; 97: 902-909. [PMID: 21058356]

5. Bellin MD, Freeman ML, Schwarzenberg SJ, Dunn TB, Beilman GJ, Vickers SM, Chinnakotla S, et al. Quality of Life Improves for Pediatric Patients After Total Pancreatectomy and Islet Autotransplant for Chronic Pancreatitis. Clinical gastroenterology and hepatology: the official clinical practice. Journal of the American Gastroenterological Association 2011.

6. Garcea G, Weaver J, Phillips J, Pollard CA, Ilouz SC, Webb MA, Berry DP, Dennison AR. "Total pancreatectomy with and without islet cell transplantation for chronic pancreatitis: a series of 85 consecutive patients. Pancreas 2009; 38:1-7. [PMID: 18665009]

7. Garcea G, Pollard CA, Illouz S, Webb M, Metcalfe MS, Dennison AR. Patient satisfaction and cost-effectiveness following total pancreatectomy with islet cell transplantation for chronic pancreatitis. Pancreas 2013; 42: 322-8. [PMID: 23407482]

8. Levy P, Barthet M, Mollard BR, Amouretti M, Marion-Audibert AM, Dyard F. Estimation of the prevalence and incidence of chronic pancreatitis and its complications. Gastroenterologie clinique et biologique 2006; 30:838-844. [PMID: 16885867]

9. Mitchell RM, Byrne MF, Baillie J. Pancreatitis. Lancet 2003; 361:1447-1455. [PMID: 12727412]

10. Jupp J, Fine D, Johnson CD. The epidemiology and socioeconomic impact of chronic pancreatitis. Best Practice and Research in Clinical Gastroenterology 2010; 24:219-231. [PMID: 20510824]

11. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systemic review. Pancreas 2006; 33:323-330. [PMID: 17079934]

12. Hirota M, Shimosegawa T, Masamune A, Kikuta K, Kume K, Hamada S, et al. The sixth nationwide epidemiological survey of chronic pancreatitis in Japan. Pancreatology 2012; 12:79-84. [PMID: 22487515]

13. Warshaw AL, Banks PA, Fernandez-Del Castillo C. AGA technical review: treatment of pain in chronic pancreatitis. Gastroenterology 1998; 115:765-776. [PMID: 9721175]

14. Tinto A, Lloyd, DA, Kang JY, Majeed A, Ellis C, Williamson RC, Maxwell JD. Acute and chronic pancreatitis--diseases on the rise: a study of hospital admissions in England 1989/90-1999/2000. Alimentary Pharmacology & Therapeutics 2002; 16:2097-2105. [PMID: 12452943]

15. World Health Organisation. Global Status Report on Alcohol and Health 2011http://www.who.int/substance_abuse/publications/global_alcohol_report/en/.

16. Otsuki M. Chronic pancreatitis in Japan: epidemiology, prognosis, diagnostic criteria, and future problems. Journal of Gastroenterol 2003; 38:315-326. [PMID: 12743770]

17. Yadav D, Timmons L, Benson JT. Incidence prevalence and survival of chronic pancreatitis: a population-based study. American Journal of Gastroenterology 2011; 106: 2192-2199. [PMID: 21946280]

18. Dite P, Stary K, Novotny I, Precechtelova M, Dolina J, Lata J, *et al*. Incidence of chronic pancreatitis in the Czech Republic. European Journal of Gastroenterology and Hepatology 2001; 13:749-750. [PMID: 11434607]

19. Bradley EL. Long-term results of pancreatojejunostomy in patients with chronic pancreatitis. American Journal of Surgery 1987; 153:207-213. [PMID: 3812895]

20. Wehler M, Reulbach U, Nichterlein R, Lange K, Fischer B, Farnbacher M, Hahn EG, Schenider T. Health-related quality of life in chronic pancreatitis: a psychometric assessment. Scandinavian Journal of Gastroenterology 2003; 38:1083-1089. [PMID: 14621285]

21. Wehler M, Nichterlein R, Fischer B, Farnbacher M, Reulbach U, Hahn EG, Schenider T. Factors associated with health-related quality of life in chronic pancreatitis. American Journal of Gastroenterology 2004; 99:138-146. [PMID: 14687155]

22. Witzigmann H, Max D, Uhlmann D, Geissler F, Ludwig S, Schwarz R, Krauss O, Lohman T, Keim V, Hauss J. Quality of life in chronic pancreatitis: a prospective trial comparing classical Whipple procedure and duodenum-preserving pancreatic head resection. Journal of Gastrointestinal Surgery 2002; 6:173-9. [PMID: 11992802]

23. Di Magno MJ, Di Magno EP. Chronic pancreatitis. Current Opinion in Gastroenterology 2006; 22: 487-497. [PMID: 16891879]

24. Lowenfels AB, Sullivan T, Fiorianti J, Maisonneuve P. The epidemiology and impact of pancreatic diseases in the United States. Current Gastroenterology Reports 2005; 7:90-95. [PMID: 15802095]

25. Beckwith J, Nyman JA, Flanagan B, Schrover R, Schuurman HJ. A health economic analysis of clinical islet transplantation", Clinical Transplantation 2012; 26:23-33. [PMID: 21323736]

26. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas. Gastroenterology 2009; 136:1134-1144. [PMID: 19245868]

27. Health and Social Care Information Centre. Hospital Episode Statistics 2009/2010. http://www.hscic.gov.uk/hes.

28. Jaakkola M, Nordback I. Pancreatitis in Finland between 1970 and 1989. Gut 1993; 34:1255-1260. [PMID: 8406164]

29. Johnson CD, Hosking S. National statistics for diet, alcohol consumption, and chronic pancreatitis in England and Wales, 1960-88. Gut 1991; 32:1401-1405. [PMID: 1752477]

30. Yang AL, Vadhavkar S, Singh G, Omary MB. Epidemiology of alcohol-related liver and pancreatic disease in the United States. Archives of Internal Medicine 2008; 68:649-656. [PMID: 18362258]

31. Mullady DK, Yadav D, Amann ST, O'Connell MR, Barmada MM, Elta GH, Scheiman JM, Wamsteker EJ, et al. NAPS2 Consortium. Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: a prospective cohort study. Gut 2011; 60:77-84. [PMID: 21148579]

32. Phillips CJ, Harper C. The economics associated with persistent pain. Current Opinions in Supportive Palliative Care 2011; 5: 127-130.

33. Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. Pain 2006; 125:172-179. [PMID: 16842922]

34. Diabetes in the UK: Key statistics on diabetes. 2010; Available at: www.diabetes.org.uk.

35. Economic Costs of Diabetes in the U.S. in 2007. Diabetes Care 2008; 31:596–615. [PMID: 18308683]

36. Choudhuri G, Lakshmi CP, Goel A. Pancreatic diabetes. Tropical Gastroenterology 2009; 30:71-75. [PMID: 19760988]

37. Health and Social Care Information Centre. Prescribing for Diabetes in England - 2005-2006 to 2010-2011. http://www.hscic.gov.uk/pubs/prescribingfordiabetes05-11.

38. Ahmed SA, Wray C, Rilo HL, Choe KA, Gelrud A, Howington JA, Lowy AM, Matthews JB. Chronic pancreatitis: recent advances and ongoing challenges. Current Problems in Surgery 2006; 43:127-238. [PMID: 16530053]

39. Neal CP, Dennison AR, Garcea G. Surgical therapy in chronic pancreatitis. Minerva Gastroenterologica Dietologica 2012; 58:377-400. [PMID: 23207614]

40. Sutherland DE, Matas AJ, Najarian JS. Pancreatic islet cell transplantation. The Surgical clinics of North America 1978; 58:365-382. [PMID: 418514]

41. Farney AC, Najarian JS, Nakhleh RE, Lloveras G, Field MJ, Gores PF, Sutherland DE. Autotransplantation of dispersed pancreatic islet tissue combined with total or near-total pancreatectomy for treatment of chronic pancreatitis. Surgery 1991; 110:427-37. [PMID: 1858051]

42. Linetsky E, Selvaggi G, Bottino R, Kong SS, Qian T, Alejandro R, Ricordi C. Comparison of collagenase type P™ and Liberase™ during human islet isolation using the automated method. Transplantation Proceedings 1995; 27:3264.

43. Linetsky E, Bottino R, Lehmann R, Alejandro R, Inverardi L, Ricordi C. Improved human islet isolation using a new enzyme blend, liberase. Diabetes 1997; 46:1120-1123. [PMID: 9200645]

44. Ammann RW, Heitz PU, Kloppel G. 1Course of alcoholic chronic pancreatitis: a prospective clinicomorphological long-term study. Gastroenterology 1996; 111:224-231. [PMID: 8698203]

45. Kobayashi T, Manivel JC, Bellin MD, Carlson AM, Moran A, Freeman ML, Hering BJ, Sutherland DE. Correlation of pancreatic histopathologic findings and islet yield in children with chronic pancreatitis undergoing total pancreatectomy and islet autotransplantation. Pancreas 2010; 39:57-63. [PMID: 19745778]

46. Wilson GC, Ahmad SA, Schauer DP, Eckman MH, Abbott DE. Cost-effectiveness of total pancreatectomy and islet cell autotransplantation for the treatment of minimal change chronic pancreatitis. J Gastrointest Surg 2015; 19:46-55. [PMID: 25095749]

47. Wilson GC[1], Sutton JM, Abbott DE, Smith MT, Lowy AM, Matthews JB, Rilo HL, Schmulewitz N, et al. Long-term outcomes after total pancreatectomy and islet cell autotransplantation: is it a durable operation? Ann Surg 2014; 260:659-65. [PMID: 25203883]

48. Wilson GC, Sutton JM, Smith MT, Schmulewitz N, Salehi M, Choe KA, Brunner JE, Abbott DE, et al. Total pancreatectomy with islet cell autotransplantation as the initial treatment for minimal-change chronic pancreatitis. HPB (Oxford) 2015; 17:232-8. [PMID: 25297689]

49. Webb MA, Illouz SC, Pollard CA, Gregory R, Mayberry JF, Tordoff SG, Bone M, Cordle CJ, et al. Islet auto transplantation following total pancreatectomy: a long-term assessment of graft function. Pancreas 2008; 37:282-287. [PMID: 18815550]

50. Sutton JM, Schmulewitz N, Sussman JJ, Smith M, Kurland JE, Brunner JE, Salehi M, et al. Total pancreatectomy and islet cell autotransplantation as a means of treating patients with genetically linked pancreatitis. Surgery 2010; 148:676-85. [PMID: 20846557]

51. Bellin MD, Sutherland DE. Pediatric islet autotransplantation: indication, technique, and outcome. Current Diabetes Reports 2010; 10:326-331. [PMID: 20680524]

52. Dong M, Parsaik AK, Erwin PJ, Farnell MB, Murad MH, Kudva YC. Systematic Review and Meta-analysis: Islet Autotransplantation after Pancreatectomy for Minimizing Diabetes. Clinical Endocrinology 2011; 75:771-9. [PMID: 21605156]

53. Walsh RM, Saavedra JR, Lentz G, Guerron AD, Scheman J, Stevens T, Trucco M, Bottino R, Hatipoglu B. Improved quality of life following total pancreatectomy and auto-islet transplantation for chronic pancreatitis. Journal of Gastrointestinal Surgery 2012; 16:1469-77. [PMID: 22673773]

54. Takita M, Shahbazov R, Kunnathodi F, Kanak M, Lawrence M, Kim P, Onaca N, Burdick J, et al. The global benefit of islet autotransplantation following total pancreatectomy on patient quality of life. Transplantation 2013; 96: 6S: S58.

55. Takita M, Naziruddin B, Matsumoto S, Noguchi H, Shimoda M, Chujo D, Itoh T, Sugimoto K, et al. Implication of pancreatic image findings in total pancreatectomy with islet autotransplantation for chronic pancreatitis. Pancreas 2011; 40:103-8. [PMID: 20881896]

56. Rilo H, Delbridge M, Beltran del Rio M, Galvani C, Rana A, Porubski M, Gruessner A, et al. Results from 55 open and robot-assisted pancreatectomies with autologous islet transplantation for the prevention of surgically induced diabetes. Transplantation 2013; 96:6S, S8.

57. Agarwal A, Langman L, Brayman K. Autologous islet cell transplantation for treatment of chronic pancreatitis; The five year University of Virginia experience. Transplantation 2013; 96:6S, S22. [PMID:]

58. Maniadakis N, Gray A. The economic burden of back pain in the UK. Pain 2000; 84:95-103. [PMID: 10601677]

59. Dite P, Ruzicka M, Zboril V, Novotny I. A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. Endoscopy 2003; 35:553-558. [PMID: 12822088]

60. Cahen DL, Gouma DJ, Nio Y, Rauws EA, Boermeester MA, Busch OR, *et al.* Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. New England Journal of Medicine 2007; 356: 676-684. [PMID: 17301298]

61. Cahen DL, Gouma DJ, Nio Y, Rauws EA, Boermeester MA, Busch OR, *et al*. Surgical drainage of the pancreatic duct in patients with chronic pancreatitis is more effective than endoscopic drainage: randomized trial. Ned Tijdschr Geneeskd 2007; 151:2624-2630. [PMID: 18161265]

62. Ihse I, Borch K, Larsson J. Chronic pancreatitis: results of operations for relief of pain. World J Surg 1990; 14:53-58. [PMID: 2407038]

63. Nealon WH, Thompson JC. Progressive loss of pancreatic function in chronic pancreatitis is delayed by main pancreatic duct decompression. A longitudinal prospective analysis of the modified Puestow procedure. Ann Surg 1993; 217:458-66. [PMID: 8489308]

64. Buchler MW, Friess H, Bittner R, Roscher R, Krautzberger W, Muller MW, Malfertheiner P, Beger HG. Duodenum-preserving pancreatic head resection: Long-term results". Journal of Gastrointestinal Surgery 1997; 1:13-19. [PMID: 9834325]

65. Frey CF, Suzuki M, Isaji S, Zhu Y. Pancreatic resection for chronic pancreatitis. The Surgical Clinics of North America 1989; 69:499-528. [PMID: 2658161]

66. Beger HG, Buchler M, Bittner RR, Oettinger W, Roscher R. Duodenum-preserving resection of the head of the pancreas in severe chronic pancreatitis. Early and late results. Annals of Surgery 1989; 209:273-278. [PMID: 2923514]

67. Bloechle C, Izbicki JR, Knoefel WT, Kuechler T, Broelsch CE. Quality of life in chronic pancreatitis--results after duodenum-preserving resection of the head of the pancreas. Pancreas 1995; 11: 77-85. [PMID: 7667246]

68. Howard TJ, Jones JW, Sherman S, Fogel E, Lehman GA. Impact of pancreatic head resection on direct medical costs in patients with chronic pancreatitis. Annals of Surgery 2001; 234: 661-667. [PMID: 11685030]

69. Schnelldorfer T, Lewin DN, Adams DB. Operative management of chronic pancreatitis: long term results in 372 patients. Journal of the American College of Surgeons 2007; 204: 1039-45. [PMID: 17481536]