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

Ashley R Dennison, Giuseppe Garcea

Department of Hepato-Pancreato-Biliary Surgery, University Hospitals of Leicester, Gwendolen Road, Leicester, LE5 4P, UK

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.

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**

\[ C^{\text{total}} = n \times \text{Individual}^{\text{total}} \]

\[ (\text{Direct} + \text{Indirect})^{\text{total}} = n \times (\text{Direct} = \text{Indirect})^{\text{ind}} \]

\[ n = \text{population/prevalence} \]

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

**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.

**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 Lowsenfels 2013).
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.
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
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 Cincinnati [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 initial 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
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
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**


