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# Blood glucose control and risk of progressing to a diabetic state during clinical follow up after cephalic duodenopancreatectomy

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A B S T R A C T

*Introduction:* Pancreatic resection carries a theoretical risk of developing diabetes; however few studies have demonstrated the effect of a cephalic duodenopancreatectomy on post-operative blood glucose control.

*Material and methods:* An analysis was made of the post-operative clinical follow up of 70 patients subjected to a cephalic duodenopancreatectomy in our Hospital between March 1993 and November 2009. The surgical indication was due to primary pancreatic disease in 30 patients (21 adenocarcinoma of the pancreas, 6 chronic pancreatitis, 1 endocrine carcinoma, 1 cystadenoma and 1 complicated pseudocyst). The pancreas was not affected in the other 40 patients (24 ampullary carcinomas, 11 cholangiocarcinomas, 3 duodenal carcinomas, 1 papillary adenoma and 1 adenomatous hyperplasia of the bile duct). Data on the pre- and post-operative diabetic state were collected.

*Results:* Before resection, 49 patients (70.0%) had a normal glucose without the need for treatment. Seventeen patients required oral diabetic treatment, 3 subcutaneous insulin, and only one was treated by diet. The duodenopancreatectomy worsened glucose control in 47.1% of the patients (23 of the previously non-diabetics and 10 of those treated with oral diabetics). Glucose control was worse when the surgical indication was due to primary involvement of the gland (progression of 63.3%) compared with patients with disease (progression of 35.0%) (P<.05).

*Conclusions:* Our results show that resection of the head of the pancreas favours the appearance of post-operative diabetes, particularly when the surgical indication is due to primary pancreatic involvement.



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## Control glucémico y riesgo de progresión del estado diabetológico durante el seguimiento clínico tras duodenopancreatectomía cefálica

*Palabras clave:*
Control glucémico
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RESUMEN

*Introducción:* La resección pancreática supone un riesgo teórico de desarrollo de diabetes; no obstante, son escasos los estudios que han mostrado el efecto de la duodenopancreatectomía cefálica en el control glucémico postoperatorio.

*Material y métodos:* Se revisó el seguimiento clínico postoperatorio de 70 pacientes sometidos a duodenopancreatectomía cefálica entre marzo de 1993 y noviembre de 2009 en nuestro hospital. La indicación quirúrgica se debió a enfermedad primaria pancreática en 30 casos (21 adenocarcinomas de páncreas, 6 pancreatitis crónicas, 1 carcinoma endocrino, 1 cistoadenoma y 1 seudoquiste complicado). En los restantes 40 pacientes el páncreas no estaba afectado (24 carcinomas ampulares, 11 colangiocarcinomas, 3 carcinomas duodenales, 1 adenoma de la papila y 1 hiperplasia adenomiomatosa de la vía biliar). Se recogieron los datos del estado diabetológico pre y postoperatorio.

*Resultados:* Antes de la resección, 49 pacientes (70,0%) eran normoglucémicos sin necesidad de tratamiento. Diecisiete pacientes requerían tratamiento antidiabético oral, 3 insulina subcutánea y sólo uno era tratado mediante dieta. La duodenopancreatectomía deterioró el control glucémico en el 47,1% de los pacientes (23 de los previamente no diabéticos y 10 de los tratados con antidiabéticos orales). El control glucémico fue peor cuando la indicación quirúrgica se debió a una afección primaria de la glándula (progresión del 63,3%) en comparación con los pacientes con patología (progresión del 35,0) ($p < 0,05$).

*Conclusiones:* Nuestro estudio revela que la resección de la cabeza pancreática favorece la aparición de diabetes postoperatoria, especialmente cuando la indicación quirúrgica se debe a una afección primaria del páncreas.



## Introduction

Although the aggressive nature of cephalic duodenopancreatectomy (CDP) has been well demonstrated, morbidity and mortality rates have decreased substantially since the procedure was described by Whipple[1] and Kausch.[2] The immediate post-operative complications are well-known and have been well documented[3-6]; however, although it would seem logical that surgery of the pancreatic gland might also affect its endocrine function, there is little data about the effect that resection of the head of the pancreas has on long-term blood glucose control. Most of the beta cells of the Langerhans islets are located in the pancreatic tail so the appearance of diabetes mellitus as the result of the removal of pancreatic tissue is a likely outcome after a body-tail resection. However, little is known about how the Whipple procedure can affect blood glucose control and whether this effect might be different, depending on whether resection of the head of the pancreas is indicated to treat a primary disease of the gland. The risk of developing diabetes after surgery and a lifelong insulin treatment is one of issues which patients often ask about prior to the intervention. Therefore, surgeons must know the risk of carbohydrate intolerance developing. In this study we analysed the probability of the appearance of diabetes mellitus and progression in terms of the need for hypoglycaemic treatment after CDP.

## Material and methods

We conducted a retrospective review of the follow-up data for patients undergoing CDP in our hospital from March 1993 to November 2009. The patients who died during the immediate post-operative period or were lost for follow-up purposes were excluded. Data was collected from 70 patients with an average age ± standard deviation of 60.4±11 years (range 31 to 84 years). Thirty men and 40 women underwent surgery. CDP was performed following a diagnosis of primary pancreatic disease in 30 patients (21 pancreatic adenocarcinomas, 6 cases of chronic pancreatitis, one endocrine carcinoma, one mucinous cystadenoma of the pancreatic head and one patient who underwent surgery for a pseudocyst complicated by a massive intracystic haemorrhage). In the remaining 40 cases the pancreatic gland was not primarily affected and the neoplasia leading to the CDP was located in other structures in the bilio-pancreatic junction (24 ampullary adenocarcinomas, 11 cholangiocarcinomas of the distal bile duct, 3 duodenal adenocarcinomas, a villous adenoma of the ampulla of Vater and one case of adenomyomatous hyperplasia of the bile duct). Fifty-eight patients underwent a Whipple-type CDP (82.9%), while 12 patients underwent a CDP with pyloric preservation. The diabetic status of the patients was recorded in the pre-operative period and during their post-operative outpatient follow-up visits. During the patients' pre-operative examination, their medical history was analysed and it was determined whether a previous diagnosis of diabetes mellitus had been made by their family doctor, endocrinologist or a specialist in internal medicine. For such cases, the type of treatment received to control blood glucose was recorded. Patients who had not presented abnormal blood glucose levels and who had therefore not required treatment were regarded as non-diabetic. Cases of

pancreatic endocrine insufficiency were divided into patients with blood glucose controlled by diet alone, patients receiving treatment with oral blood glucose-lowering medications and patients requiring subcutaneous insulin to achieve normal blood glucose levels. After surgery all the patients who maintained abnormal blood glucose levels while they were in hospital were assessed before being discharged by an endocrinologist in order to prepare patients for their future therapy. Subsequent outpatient blood glucose control was the responsibility of their family doctors. Average post-operative follow-up at external surgery appointments was 47.27 months, although the progression of diabetic status was only analysed if it appeared during the first year after surgery so as not to include non-surgical causes as the reason for deterioration in blood glucose control. All the patients who were analysed were followed up for at least 1 year, except for 9 patients who died as a result of tumour relapse before completing their 12 months of follow up. For these patients, their last available blood glucose control prior to their death was analysed. Progression of diabetic status was defined as the need to introduce a blood glucose treatment or control measure during post-operative clinical follow-up in patients who had not previously been diabetic or when patients who already presented some degree of pre-operative carbohydrate intolerance had to go up one step on the therapeutic scale (diet/oral hypoglycaemic agents/insulin). The decision to introduce a treatment to control or modify blood glucose was made by the patient's family doctor or the relevant endocrinologist. The statistical significance of the differences which were found was analysed by means of a chi-squared test for qualitative variables and a non-parametric Mann-Whitney test for quantitative variables.

## Results

Before surgery 49 patients (70.0%) had satisfactory blood glucose control without the need for treatment. Amongst the patients who were diagnosed with diabetes before the intervention, only one (1.4%) had carbohydrate intolerance that was being treated by diet and 3 patients (4.3%) were already being treated with insulin due to type 1 diabetes mellitus. The other 17 patients (24.3%) were receiving routine treatment with oral anti-diabetic agents to maintain normal blood glucose levels. Pre-operative endocrine function is shown in Table 1.

Pancreatectomy led to a progression in diabetic status in 33 patients (47.1% of the total). In 23 previously non-diabetic patients (46.9% of the non-diabetic series) and in 10 patients who were previously treated with oral hypoglycaemic drugs (58.8% of the patients treated with anti-diabetic agents) a progression in diabetic status was detected, although the differences were not statistically significant. Amongst the patients who had normal blood glucose levels prior to the intervention, 20.4% of the total required insulin treatment following surgery, 8.2% required oral anti-diabetic drugs and 18.4% were treated with dietary restrictions (Table 2).

It was more common for blood glucose control to worsen in patients in whom pancreatic resection was performed to treat primary pancreatic disease (63.3% of diabetic status progression), compared with patients who underwent CDP for an extrapancreatic neoplasia (35.0% of diabetic progression), which was a statistically significant difference ($P<.05$). In all the patients with chronic pancreatitis their blood glucose control deteriorated and in 52.4% of patients with pancreatic adenocarcinoma endocrine insufficiency progressed (Table 3).

With regard to the progression of diabetic status, there were no differences that reflected the surgical technique that was employed (48.3% after Whipple-type CDP and 41.7% following CDP with pyloric preservation). The development of diabetes after pancreatic resection was not related to age at the time of the intervention ($P>.05$).

## Discussion

CDP is an aggressive intervention which is still associated with high levels of morbidity and mortality. Given that it is the immediate post-operative complications that largely determine the likelihood of short- and long-term survival, most studies only concentrate on analysing early morbidity. However, there

**Table 1 – Pre-operative diabetic status classified according to diagnosis and surgical indication**

| Diagnosis | Pre-operative diabetic status | | | |
|---|---|---|---|---|
| | No diabetes | Treatment with insulin | Treatment with OAD | Treatment by diet alone |
| Adenocarcinoma of the pancreas | 19 (52.4%) | 1 (4.8%) | 8 (38.1%) | 1 (4.8%) |
| Chronic pancreatitis | 6 (100%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Pancreatic pseudocyst | 1 (100%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Pancreatic cystadenoma | 1 (100%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Pancreatic endocrine carcinoma | 0 (0%) | 1 (100%) | 0 (0%) | 0 (0%) |
| Ampulloma | 18 (75%) | 0 (0%) | 6 (25%) | 0 (0%) |
| Villous adenoma of the papilla | 0 (0%) | 0 (0%) | 1 (100%) | 0 (%) |
| Cholangiocarcinoma | 9 (81.8%) | 1 (9.1%) | 1 (9.1%) | 0 (0%) |
| Duodenal cancer | 2 (66.7%) | 1 (33.3%) | 0 (0%) | 0 (0%) |
| Adenomyomatous hyperplasia of the bile duct | 1 (100%) | 0 (0%) | 0 (0%) | 0 (0%) |

OAD indicates oral anti-diabetic agents.

**Table 2 – Pre- and post-operative diabetic status**

| | Post-operative diabetic status | | | |
|---|---|---|---|---|
| | Non-diabetic | Treatment by diet alone | Treatment with OAD | Treated with insulin |
| *Pre-operative diabetic status* | | | | |
| Non-diabetic (n=49) | 26 (53.1%) | 10 (20.4%) | 4 (8.2%) | 9 (18.4%) |
| Treated by diet alone (n=1) | 0 (0%) | 1 (100%) | 0 (0%) | 0 (0%) |
| Treated with OAD (n=17) | 0 (0%) | 0 (0%) | 7 (41.2%) | 10 (58.8%) |
| Treated with insulin (n=1) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (100%) |

OAD indicates oral anti-diabetic agents.

**Table 3 – Progression of diabetic status according to diagnosiss**

| Diagnosis | Progression of diabetic status | | | |
|---|---|---|---|---|
| | No progression | | Progression | |
| *Primary pancreatic disease (n=30)* | | 11 (36.7%) | | 19 (63.3%) |
| Adenocarcinoma of the pancreas | 10 (47.6%) | | 11 (52.4%) | |
| Chronic pancreatitis | 0 (0%) | | 6 (100%) | |
| Endocrine carcinoma | 0 (0%) | | 1 (100%) | |
| Pancreatic pseudocyst | 0 (0%) | | 1 (100%) | |
| Pancreatic cystadenoma | 1 (100%) | | 0 (0%) | |
| *Extra-pancreatic disease (n=40)* | | 26 (65.0%) | | 26 (65.0%) |
| Ampulloma | 15 (62.5%) | | 9 (37.5%) | |
| Villous adenoma of the papilla | 1 (100%) | | 0 (0%) | |
| Cholangiocarcinoma | 8 (72.7%) | | 3 (27.3%) | |
| Duodenal carcinoma | 2 (66.7%) | | 1 (33.3.0%) | |
| Adenomyomatous hyperplasia of the bile duct | 0 (0%) | | 1 (100%) | |

are few studies which analyse the endocrine insufficiency that may develope after surgery and that significantly compromises quality of life. A review of the scientific literature shows that the extension of the pancreatic resection is the chief factor involved in post-operative pancreatic endocrine insufficiency,[7] showing that distal pancreatectomy is associated with a higher risk of changes in carbohydrate metabolism.[8,9] Despite this, our study reveals that pancreatic head resection can also favour the development of diabetes mellitus as a result of pancreatic loss. Most of the studies which analyse blood glucose control following a pancreatectomy have been conducted on patients diagnosed with chronic pancreatitis,[10,11] so it can be deduced that the deterioration in blood glucose control and the development of diabetes mellitus are not exclusively related to the resection of insulin-producing cells during pancreatectomy, but are also partially related to the previous destruction of these cells as a result of a chronic inflammatory process, which limits the pancreatic reserves which are available after surgery. Our study agrees with previously published data, as all the patients with chronic pancreatitis had normal blood glucose levels before surgery but required some form of treatment to control their hyperglycaemia after the intervention.

The link between diabetes mellitus and pancreatic cancer has been a subject of debate for years. The mechanism by means of which pancreatic cancer might be involved in hyperglycaemia is poorly understood. Amongst other factors, an increase in peripheral resistance to insulin, the suppression of insulin secretion, changes in the conversion of proinsulin into insulin and even a change in nutritional habits and carbohydrate metabolism have been suggested.[12] Our results reveal that 47.6% of the patients diagnosed with adenocarcinoma of the pancreas show some kind of change in carbohydrate metabolism prior to surgery. This means there is a much higher incidence amongst all the patients who undergo a CDP, although not all of them presented hyperglycaemias of recent onset. In our study we did not find an improvement in blood glucose control following pancreatectomy to treat pancreatic cancer, as other authors have suggested.[13] On the contrary, the patient group with malignant pancreatic disease showed the second highest percentage of progression of post-operative pancreatic endocrine insufficiency, 52.4% of patients being affected. It is hardly surprising that patients with a diseased pancreas, albeit a malignant or chronic inflammatory condition, had a greater tendency to present with poor blood glucose control during post-operative clinical follow-up, compared with patients undergoing surgery for extrapancreatic pathologies. Resection of part of the pancreas may be enough to develop diabetes due to loss of pancreatic tissue when the reserves of beta cells are limited. However, over a third of these patients developed post-operative hyperglycaemia requiring treatment, which highlights the risk of diabetes appearing after CDP, even in patients with a healthy pancreas.

It has been reported that post-operative endocrine function might be less affected after a CDP with pyloric preservation, which has provided additional arguments to those who defend the view that it should be the technique of choice when considering resection of the head of the pancreas.[14-16] However, once again, these studies have been conducted on patients with chronic pancreatitis, which means the results could be influenced by a status in which the gland is already predisposed to diabetes. In our experience, the resection technique had no influence on post-operative endocrine function.

It has been claimed that resections of less than 80% of the distal part of the pancreas, where the highest density of beta cells is concentrated, result in a reduced risk of the development of diabetes,[17] but our results show how smaller resections, those affecting the head of the pancreas, where the density of insulin-producing cells is considered to be lower, are associated with an important risk of post-operative hyperglycaemia requiring some form of treatment. Going beyond specific biochemical studies which analyse the modification of certain parameters of endocrine function during post-operative recovery from a CDP, such as C-peptide or glycosylated haemoglobin, our study presents pragmatic data about the real need for insulin or oral hypoglycaemic treatment after surgery. For the patient who has to think about undergoing a pancreatic resection when faced with a diagnosis which is often uncertain, knowing the real risk of developing diabetes becomes very important. Although the literature admits up to 20% or more of non-tumoral disease in resection pieces taken from patients undergoing CDP, owing to suspected malignancy,[18] our series showed this figure to be 14.3%. However, up to a quarter of patients whose blood glucose control worsened following surgery had a benign disease and required longlife treatment which they did not previously need. Our study is retrospective and, perhaps, the indications of progression in treatment for blood glucose control were not homogeneous for all the patients and even, as happens in routine clinical practice, the patients may have been undertreated with oral anti-diabetic drugs when they really needed insulin. This is precisely why the results of our study can be extrapolated to routine clinical practice, in which the surgeon is not normally responsible for the outpatient blood glucose control, so he/she does not makes the decision to administer insulin. However, he/she is responsible for informing the patient during the pre-operative phase and establishing indications for resection. The information that patients really demand is to know whether they are going to develop diabetes after surgery and if they will require insulin treatment for the rest of their life. The pancreatic surgeon must know the real risk of requiring chronic post-operative treatment to achieve blood glucose control in patients undergoing CDP so that he/she can inform patients about all the immediate post-operative and long-term consequences of the procedure, analysing not only the benefits of the procedure but also its consequences, which are often irreversible.

## Conflict of interest

The authors declare that they have no conflict of interest.

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