Insulin treatment in an obese patient and a secondary diabetes due to pancreatectomy

Tratamiento con insulina en un paciente obeso y con diabetes secundaria a pancreatectomía

Male aged 41, obese, with secondary diabetes to pancreatectomy, which is not able to control it adequately. He is professor of religion and has never done physical exercise.

Personal history
In the year 2003 part of the pancreas was extirpated since it showed a neuroendocrine carcinoma which produced gastrin, which was later treated with lanreotide. He received the last dose before his arrival to our center, and in the record it mentioned that the patient found himself with radiological stability and with a decrease of markers. Generalized epilepsy since he was ten years old with a treatment of sodium valproate and carbamazepine.

Actual disease
As consequence of the pancreatic intervention, which left him only a rest of the pancreas head, the patient developed diabetes that was treated with insulin from the beginning. When arriving at our site, he was under treatment with insulin glargine 88 IU/day and insulin glulisine 6 IU before each meal, with adjustments according to pre-prandial capillary glycemias, together with metformin (2,550 mg/day) and pioglitazone (30 mg/day). He rarely carried out postprandial glycemia. When asked about his metabolic control, he did not know the HbA1c value and said not knowing what this parameter is about. He submits a report from his physician corresponding to the month previous to his arrival, in which a value of 8.3% can be observed in the HbA1c. The patient had already attended our site a year before an in his analytics an HbA1c of 8.5% could be appreciated as well as a C-peptide of 0.7 ng/mL, as well as hyperlipidemia and hyperuricemia, with normal hepatic and renal function. He undergoes treatment with bromozepan, omeprazol, fenofibrate and lanreotide 120 mg in autogel (1 ampule each 28 days), besides his hypoglycemic treatment, of valproic acid and carbamazepine.

The exploration stresses a weight of 111.9 kg, height 171 cm, blood pressure (BP) 150/85 mmHg and abdominal perimeter 118 cm. Neither peripheral vascular disorder nor peripheral neuropathy signs can be observed.

Introduction. Therapeutic objectives in this patient
The diabetes resulting from the pancreatectomy is according to the mechanism, the prototype of the second-
of glucagon, the glucose turnover and the considerably reduced glycogenesis, as well as the adrenalin release in response to the altered hypoglycemia, and c) impairment of the insulin resistance, that might worsen with the administration of glucagon. All this obliges the preference to a less strict metabolic control than in patients with a functioning pancreatic tissue.

The high concentration of islets in the pancreas tail suggests that a distal pancreatectomy would be worse tolerated in terms of endocrine secretion of the gland. In fact, resections of 90% are requested to produce endocrine deficit, in spite of the hypertrophy and the increase of the physiological activity of the remaining islets, what would oblige a strict insulin cover and more than a daily dose would be necessary. However, neither the intake nor the absorption of nutrients would be affected. Hormones and enzymes should be replaced after a total pancreatectomy.

The gastrinoma is a tumor that secretes gastrine, responsible of the great hypergastrinemia of the Zollinger-Ellison syndrome, characterized by refractory peptic ulcer, diarrhea and steatorrea. Of very low prevalence (1-4 per 1 million of people); it appears between 50 and 60 years of age, usually in women more than in men (3:1). It is localized in the pancreas in 40% and in the duodenal wall in the other 40%. It can be associated to the MEN-1 syndrome (20-25%) and it is then frequently malignant. In our case, the patient is obese on whom it can be considered an insulin peripheral resistance condition and other factors of cardiometabolic risk, as the dyslipemia.

The level of the C-peptide is useful to have an idea of the insulin reserve, considering that the exogenous insulin inhibits the production of endogenous insulin by the conserved pancreatic tissue.

Which are the modifications you would do in the hypoglycemiant treatment? Do you consider adequate to keep the insulin-sensibility drugs in this patient? Which are the most adequate glycemic controls?

There is a marked resistance to the action of the insulin in the obese patient closely related to the adipose tissue and, especially, to the abdominal deposit or centripetal.

In the postabsorptives phases, the exogenous load of glycemia is not captured adequately by the insulin-dependent tissues (adipose and muscular) and the main mechanism of the hyperglycemia is postprandial. This alteration suggests a stimulus for the release and the hepatic synthesis of glucose as of the glycogenolysis and the glyco-

eogenesis.

The thiazolidinediones improve the glycemic control when acting as sensitizing agents to the insulin and as reducers of the hepatic glycogenogenesis. Its clinical efficiency is in clear relation to the presence of a conserved insulin reserve; therefore it is only useful in patients with functioning pancreas. So, it would be feasible to withdraw the pioglitazone in this case.

The biguanides improve the sensitivity to insulin and reduce the hepatic production of glucose when reducing both the glycogenogenesis and the glyco-

sylated hemoglobin (HbA1c) (2%) with doses of 2,000 mg, without obtaining additional reductions when reaching the dose of 2.500 mg.

In our case, the patient is with a very high dose of slow analogue and does not know what is HbA1c, so the controls up to date have exclusively been based in the pre-

prandial values of glycemia. It is logical to think that such values are close to normality. When the treatment has to be intensified in a diabetic patient, it is necessary to perform capillary controls with 6 determinations, 3 pre-

prandial and 3 postprandial. The value of HbA1c of 8.3% has to be very influenced by the postprandial glycemia, whose values we do not know about.

After the performance of the profiles, we will encounter probably one of the following assumptions:

• High basal and postprandial glycemias. We could keep the same type of insulin or, what is more logical, due to the high units of insulin glargine that are admin-
istered, to use a slow analogue that allows two daily shots (as the insulin detemir), distributing the total dose to 50% in each one, and increasing the units until keeping reasonable basal glycemias. We should add fast analogue considering the postprandial peaks and we would keep the metformin for the already mentioned reasons. A second alternative would be to use the mixture 30/70 with rescue of fast analogue in the midday meal. The total dose of the mixture should be reduced a 20-30% as regards to the dose of the total basal analogue and then adjust according to the later profiles. This guideline would be of easy application if the patient keeps a stable life rhythm, with adequate food and scheduled as regards timetables.

**Normal basal glycemias with high postprandial peaks.** We would keep the same slow analogue and adjust only with the fast analogues. This is a useful technique if we encounter a patient with irregularities regarding to the number of intakes a day and their timetable.

**Which other therapeutic modifications would you carry out?**

This patient shows a blood pressure (BP) of 150/85 mmHg. The diabetic patients are considered of high risk as from the BP values over 130/80 mmHg. For the reduction of the pressure values in a patient with diabetes, the blockage of the rennin-angiotensin system should be always placed in the first therapeutic step, though the need to associate drugs in most of the cases is recognized. The intense reduction has beneficial and consistent effects in the reduction of the global mortality and cardiovascular cause, as well as the ictus incidence, coronary disease, cardiac disorder and cardiovascular events in general. The ADVANCE study proved in the same way that the reduction of the systolic blood pressure up to values of 134 mmHg with the use of a combination with angiotensin-converting enzyme inhibitors (ACEI) and an added diuretic to the usual treatment, had beneficial effects in preventing the cardiovascular morbimortality, with a reduction even in the global mortality that reached the 14%. A key aspect should be added to the medical treatment that might consolidate the adequate metabolic control: the diabetological education with nursing support. It would allow obtaining basic knowledge about the diet, about the techniques of insulin injections, the recognition of alarm symptoms regarding to possible hypoglycemies and how to neutralize them, about the use of glucagon and the action in relation to the punctual hypoglycemies.

**Acknowledgements**

My sincere gratitude to Dr. Pilar Martín Vaquero, without her support, though at distance, this work could not have appeared.

**Declaration of potential conflict of interest**

Ezequiel Arranz received feed for conferences about the use of the DPP-IV inhibitors in type 2 diabetes mellitus by the MSD laboratories.

**References**

Which are the therapeutic objectives you would indicate for this patient?

In an oncological patient, a determining factor when deciding the therapeutic objectives is the vital prognosis at long term. There are several factors that condition the survival of the sporadic gastrinoma. From these, probably the most important one is the magnitude of the metastatic disease at hepatic level and its growth speed before starting the treatment.\(^1\) The survival at 5 and 10 years of the patients with metastatic hepatic disease of slow growth might reach approximately 100% and 80%, respectively.\(^4\) On the other hand, even in patients with progressive metastatic gastrinoma and with worse prognosis, the somatostatin analogues, as the lanreotide, have demonstrated to be able to stabilize the tumor growth and, in some cases, to reduce its volume. Thus, in a study of patients with more aggressive tumors, a survival of 75% could be observed for a follow-up period between 4 and 8 years in those patients with a good response to the octreotide.\(^5\)

Therefore, for our patient, the possibilities of an extended survival are considerable. So, it seems to be reasonable to mark a glycemic control objective with glycosylated hemoglobin (HbA\(_1c\)) of 7-7.5% (mean glycemia estimated between 150-160 mg/dL). This objective allows balancing the therapeutic, psychological, economical and self-management effort with the possible clinical benefits, in a patient with certain comorbidity. On the contrary, we could mark less strict objectives in case of progression evidence or signs of inadequate prognosis during the follow-up. In the same way, we could set out a stricter glycemic control in young patients with pancreatogenic diabetes, without evidence of residual disease and without other comorbidities. In this sense, in spite that there is no data in patients with secondary diabetes, but the evidences in patients with T2D indicate clear benefits derived from a multifactorial intervention regarding to the different risk factors. The study of Gaede et al.\(^7\) is remarkable, where a reduction of approximately 50% of cardiovascular and microvascular risk events in patients with high risk T2D after a multifactorial intervention with a mean follow-up of 7.8 years. Therefore, I would mark the following objectives: BP <130/80 mmHg, LDL cholesterol (c-LDL) <100 mg/dL, HDL cholesterol (c-HDL) >40 mg/dL, triglycerides <150 mg/dL and a loss weight over 5%.

Which are the modifications you would do in the hypoglycemiant treatment?

Do you consider adequate to keep the insulin-sensibility drugs in this patient?

The diabetes secondary to pancreatic resections comes together with hormonal impairments that depend on the type of intervention, the extension and the location (discal or proximal). These alterations confer differential characteristics as regards to T1D and T2D. In wide resections, besides the insulinopenia, the deficit of glucagon might contribute to the iatrogenic hypoglycemia and the deficit of the pancreatic polypeptide contributes to the persistent hyperglycemia due to insulin-resistance at hepatic level. The impairments, on occasions, cause labile diabetes of difficult management. Likewise, in those costs, in turn of an uncertain benefit in terms of cardiovascular risk reduction. In the same way, the analysis of these studies does not predict great benefits in a uniform manner in terms of microvascular risk. A possible exception to these affirmations would be the youngest patients, with recent starting diabetes and without complications.\(^6\)

On the other hand, we are facing a patient with high cardiovascular risk, since, besides diabetes, the patients shows a level 2 obesity (body mass index [BMI]: 38.3 kg/m\(^2\)), a high waist perimeter (>102 cm), hyperuricemia, hyperlipidemia and an inadequately controlled blood pressure (150/85 mmHg). In this case, there is no data in patients with secondary diabetes, but the evidences in patients with T2D indicate clear benefits derived from a multifactorial intervention regarding to the different risk factors. The study of Gaede et al.\(^7\) is remarkable, where a reduction of approximately 50% of cardiovascular and microvascular risk events in patients with high risk T2D after a multifactorial intervention with a mean follow-up of 7.8 years. Therefore, I would mark the following objectives: BP <130/80 mmHg, LDL cholesterol (c-LDL) <100 mg/dL, HDL cholesterol (c-HDL) >40 mg/dL, triglycerides <150 mg/dL and a loss weight over 5%.

List of acronyms quoted in the text:

ACEI: angiotensin-converting enzyme inhibitors; ARA II: angiotensin-II receptor antagonists; BMI: body mass index; HbA\(_1c\): glycosylated hemoglobin; T2D: diabetes mellitus type 2.
cases that comprise intestinal resection, an impairment of the incretin secretion occurs that also has a considerable effect in the homeostasis of the glucose. On the other hand, it has to be considered the influence of the disease that motivates the pancreatectomy. For example, in patients with pancreas cancer, the clearance of the cytokine secretion by the tumor might improve the peripheral sensitivity to insulin and glucose homeostasis.

In case of distal resection, the incidence of diabetes is low, ranging between 9 and 32% considering the magnitude of the resection, the disease that motivates it and the presence or not of previous intolerance to the glucose. In this sense, it is estimated that it is sufficient to keep 20-25% of the residual pancreas to keep a clinically normal glucose homeostasis. For a pancreatectomy of the same magnitude, the most important prognosis factors of postsurgical diabetes are obesity and the pre-surgical glycemia. This indicates that factors as the previous impairment of the beta-cell function and the insulin-resistance that the obese patients show facilitate the hyperglycemia, so its correction is important. In this sense, almost 40% of the patients with distal postpancreatectomy diabetes keep an acceptable metabolic control level with oral antidiabetics (table 1).

As regards to the insulin guideline, it is interesting to assess and discuss with the patient the possibility of simpler regimes. A recent publication shows how the simplification of insulin treatment in insulinized patients with T2D and detectable C-peptide allows reducing the hypoglycemia risk without engaging the metabolic control level. Perhaps in our patient we could consider the use of 2 or 3 doses of prefixed mixtures as alternative to the bolus-basal treatment.

Another interesting aspect refers to the use of insulin glargine. It has been described that glargine induces the proliferation of osteosarcoma cell lines. In spite of the lack of data available regarding to neuro-endocrine tumors, a recent study could not objectify any effect of glargine in the growth of pancreas carcinoma cell lines nor in the survival of the patients with this disease. Probably, from this point of view, should the glargine not raise concern.

In models of diabetic animals due to pancreatectomy, exendine-4 has demonstrated to have capacity to stimulate the regeneration of the pancreas and the beta-cell expansion, through its effect on the GLP-1 receptor. Therefore, it is interesting to think about the use of treatments based on incretin in pancreatectomized patients. Moreover, the addition of vildagliptin to insulin in T2D has demonstrated a glycemic control improvement with less hypoglycemias. In our environment, this association is not authorized. On the other hand, in my opinion, it would be imprudent to use it in our patient. In this sense, it is known that there is an over-expression of GLP-1 receptors in several human tumors that might have an influence in the tumoral biology.

<table>
<thead>
<tr>
<th>Procedure (resection %)</th>
<th>Post-surgical diabetes prevalence (%)</th>
<th>Diabetic patients treated with insulin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total pancreatectomy (100%)</td>
<td>100 (75% with labile diabetes)</td>
<td>100</td>
</tr>
<tr>
<td>Almost total pancreatectomy (80-95%)</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>Distal pancreatectomy (40-80%)</td>
<td>32</td>
<td>59</td>
</tr>
<tr>
<td>Pancreatoduodenectomy (50%)</td>
<td>26</td>
<td>40</td>
</tr>
</tbody>
</table>

The percentages might vary in the different series, basically influenced by the basal disease that motivates the pancreatectomy and by the pre-surgical prevalence of alterations of the carbohydrate metabolism. Modified in Slezak and Andersen.

### Which is the type and number of glycemic controls you consider appropriate for this patient?

The patients with multiple insulin doses should undergo 3 or more daily controls. Moreover, it is recommendable to perform postprandial controls to achieve the postprandial glycemia objectives (initially, I would recommend 1 to 2 weekly profiles). Obviously, during the follow-up we should be sure that the technique is appropriate and that it has capacity to adjust the treatment according to the results.

### Which other therapeutic modifications would you perform?

I would indicate therapeutic changes in the lifestyle, with exercise and hypocaloric planned diet. I would also start an hypotensive treatment with an antagonist of the
angiotensin-II receptor antagonists (ARA II) or angiotensin-converting enzyme inhibitors (ACEI) in case of confirming a BP >130/80 mmHg during a new visit. As regards to the lipids, I would assess the possibility of adding a statin or replace the fibrate by a statin, as a preferable strategy for the control of lipids in patients over 40 years of age and one or more factors of cardiovascular risk. Moreover, I would indicate 100 mg/day of acetylsalicylic acid as a primary care prevention strategy.16

Finally, due to the antiepileptic carbamazepine and valproate have been related to weight gain and insulin-resistance, I would ask for a new specialized assessment to consider its replacement by other drugs with a more beneficial metabolic profile (for example, topiramate, zonisamide or lamotrigine).17

Declaration of potential conflict of interest
Ll. Masmiquel received feed for conferences and/or consultancy from Abbott, GSK, MSD, Lilly, Menarini, Novartis, Pfizer, Novonordisk, Sanofi-Aventis and Roche. He took also part in clinical trials sponsored by Novartis, Novonordisk, Lilly, Abbott and MSD.

References