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ORIGINAL ARTICLE

# Pancreatic beta cell function is preserved in the short term in patients with type 2 diabetes undergoing non-urgent surgery

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## ABSTRACT

BACKGROUND: Type 2 diabetes mellitus (T2DM) is a progressive condition influenced by many factors. Surgery usually produces hyperglycemia in the postoperative period, which leads to adverse clinical outcomes. Possible consequences of surgery on beta cell reserve have not been explored. The aim of this study was to assess the effect of surgery on the beta cell function of patients with T2DM undergoing non-urgent surgery.

METHODS: We performed a prospective observational study on the population of patients with T2DM scheduled for surgery in a tertiary level hospital. After adequate wash-out periods for antidiabetic medications, two blood samples were collected: one fasting and the other one six minutes after an intravenous stimulation with glucagon. Glucose, insulin and C-peptide concentrations were measured. This determination was repeated about a month after surgery.

RESULTS: We included 42 patients with the following characteristics: 47.6% males, average $HbA1_c$ 7%, average time from T2DM diagnosis 7.3 years and average age 62.1 years. Intravenous glucagon produced a significant increase in C-peptide after six minutes in both the presurgical (C-peptide values: basal 2.97 ng/mL; after glucagon 5.53 ng/mL) and the postsurgical (C-peptide values: basal 3.12 ng/mL; after glucagon 5.67 ng/mL) periods (mean difference 2.56 ng/mL and 2.55 ng/mL respectively, $P<0.001$). However, C-peptide increase after glucagon was not different between the presurgical and the postsurgical periods (2.56 ng/mL *vs.* 2.55 ng/mL, $P>0.05$).

CONCLUSIONS: The pancreatic beta reserve of patients with T2DM was not affected a month after the non-urgent surgery. The direct measurement of pancreatic function by dynamic assessment with glucagon did not change, nor did we find alterations in the indirect calculation of insulin secretion using the HOMA-B. None of these parameters reached statistical significance. Non-urgent surgical procedures included in our study are safe for patients with short lasting, properly controlled T2DM, from the point of view of glucose metabolism assessed by pancreatic insulin secretion. We can consider non-urgent surgical procedures safe from the point of view of the preservation of the pancreatic reserve in patients with T2DM. A sharp deterioration of metabolic control is not expectable in the short term for these patients, which represent a large proportion of the population undergoing surgery in modern hospitals.

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**Key words:** Diabetes mellitus, type 2 - Insulin-secreting cells - C-peptide - Surgical procedures, operative.

Type 2 diabetes mellitus (T2DM) is a very prevalent condition accounting for 90% of the total diabetic population.[1] It is estimated that by 2030 about 439 million people will be affected by diabetes, with T2DM accounting for most of the cases.[1] T2DM is produced by

a combination of insulin resistance and defects in insulin secretion on a basis of a pro-inflammatory state, usually favored by obesity. Hyperinsulinism appears initially as a compensatory measure, but it leads to a sustained cellular effort which, in time, causes the exhaustion of the pancreatic beta cells.[2]

Glycemia increases steadily and hyperglycemia can be detected either in fasting or in the postprandial state. When T2DM is diagnosed, approximately 50% of the original insulin-secreting beta cells have suffered apoptosis or dedifferentiation.[3, 4] Hence the importance of preserving the remaining beta cells to achieve an optimal metabolic control and avoiding the complications of diabetes (diabetic retinopathy, nephropathy and neuropathy) and potentially fatal cardiovascular events leading to death.[5]

In modern health services, surgery is a common procedure performed on a daily basis in every secondary or tertiary level hospital worldwide and includes a wide range of very different techniques. A high proportion of these surgical operations are performed on patients suffering from T2DM, and hyperglycemia is a frequent feature both in the presurgical and the postsurgical period.[6] This fact has prompted the interest of many investigators, who have studied the relationship between perioperative hyperglycemia and an increase in the morbidity and mortality of these patients. However, the role of surgery as a cause of decreased insulin secretion has not been investigated so far.

Richards *et al.*[7] retrospectively investigated the relationship between hyperglycemia (plasma glucose >200 mg/dL at least twice during hospital stay) and wound infections in 790 patients undergoing surgical repair of lower limbs, upper limbs and pelvis fractures. Wound infection was more frequent in hyperglycemic patients (4.4% *vs.* 1.6%, P=0.02) and hyperglycemia was considered an independent factor for wound infection after 30 days (odds ratio 2.7, 95% confidence interval 1.1-6.7). Similarly, Dronge *et al.*[8] studied the risk of infection in the postoperative period in patients with diabetes mellitus (DM). They collected data from 687 patients hospitalized in third level sanitary centers including those undergoing non-cardiac major surgery with general, spinal or epidural anesthesia, as well as carotid endarterectomies and inguinal herniorraphies. The primary aim was to assess the incidence of pneumonia, surgical wound infection, urinary tract infection or sepsis. In the regression analysis, the odds ratio was 2.13 (P=0.007) for patients with HbA1c higher than 7% compared to properly controlled diabetic patients.

Szekely *et al.*[9] explored the link between perioperative hyperglycemia and postsurgical mortality in 5050 patients undergoing cardiopulmonary bypass. Diabetic patients had a higher mortality than non diabetics (4.2% *vs.* 2.9%, P=0.02) and elevated plasma glucose of 250-300 mg/dL (odds ratio 2.56, CI 95%: 1.18-5.57) and >300 mg/dL (odds ratio 2.74, CI 95%: 1.22-6.16) were independent mortality risk factors.

In T2DM there exists an inflammatory environment which simultaneously increases cardiovascular risk and enhances the deterioration of pancreatic insulin secretion, thus creating a vicious circle.[10] Surgery is a "controlled" aggression which triggers an acute inflammatory response, so surgical procedures could have a deleterious effect on T2DM, fact from which arose the clinical question for this study.[11, 12]

The assessment of the beta cell reserve cannot be made through image techniques and histologic samples are not easily available, so biochemical methods are the preferred procedures. Measuring insulin can be difficult due mainly to analytical interferences from exogen analogs and the short live of the endogenous hormone, but there is a peptide which can be determined reliably: C-peptide. After preproinsulin is produced, it is processed in the rough endoplasmic reticulum to generate a molecule of proinsulin.[13] The latter is cleaved by endopeptidases and carboxipeptidases in insulin and C-peptide in equimolar concentrations.[14] C-peptide does not suffer such an important first-step clearance from circulation as insulin by the liver and has a longer plasmatic half-life, making it an ideal alternative to direct insulin measurement.[15]

Besides, dynamic tests usually give more

information about endocrinologic axis than isolated basal determinations, and C-peptide can be measured six minutes after intravenous stimulation with glucagon.[16, 17] This method has been widely used and has proved to be a reliable means of assessing beta cell function. Hence its selection as the best technique to determine endogenous insulin secretion. Jones *et al.*[18] published in 2013 an article where they recommend a C-peptide test after glucagon stimulation in different clinical settings: distinction between type 1 diabetes mellitus (DM1) and T2DM; identification of patients with MODY (maturity onset diabetes of the young); detection of complete insulin deficiency; assessment of treatment modifications in subjects receiving oral hypoglycemia agents or insulin; identification of patients prone to ketoacidosis; and assessment of DM response to bariatric surgery.

The goal of our study was to assess possible changes in pancreatic beta cell function in patients with T2DM undergoing scheduled surgery by comparing C-peptide secretion after intravenous glucagon infusion in two settings: before and after surgery.

## Materials and methods

We performed an observational prospective study on a complete surgical population of patients with T2DM. It was conducted between September 2012 and January 2014 in a single Spanish hospital. Inclusion criteria were: age 18-75 years and diagnosis of T2DM according to ADA/EASD criteria [19] at least one year before inclusion or treatment for T2DM. Surgical operations included by specialty were: neurosurgery (cervical and lumbar herniations, laminecthomies, foraminothomies), plastic surgery (postmastectomy reconstructions, pediculated and free skin flaps), general surgery (laparoscopic cholecystectomies, mastectomies, parathyroidectomies and thyroidectomies), vascular surgery (peripheral revascularizations, carotid thromboendarterectomies) and urology surgery (radical laparoscopic prostatectomy, laparoscopic nephrectomy, ureteral and uretral plastic surgery).

Exclusion criteria were: time of evolution of T2DM of less than 1 year from diagnosis, DM1, DM secondary to corticoid use, gestational diabetes, pregnant or lactating women and refusal of patients to participate. We intentionally excluded patients undergoing bariatric surgery or surgical techniques involving the small intestine, given the demonstrated changes in incretin secretion in these patients and the subsequent confusion it would imply when interpreting the results.[20]

Patients scheduled to undergo surgical procedures were identified by constantly checking the waiting list for surgery. Those with the diagnosis of type 2 diabetes mellitus and fulfilling the inclusion criteria were contacted through a telephonic call and invited to participate. Those subjects accepting to participate were appointed a visit at the endocrinologist's office to have the study explained. At the same time the written informed consent was signed by both the patient (or legal tutor) and the endocrinologist. The first blood test was performed a few days after the inclusion visit to determine fasting basal plasmatic plasma glucose, basal insulin and basal C-peptide through either the basilic or the cephalic forearm veins. Before obtaining blood samples, patients underwent a ten-hour nocturnal fasting period. Afterwards, glucagon (Glucagen NovoNordisk, Bagsværd, Denmark,1 mg vial) [21] was infused and another sample was obtained after six minutes to assess post-stimulus C-peptide concentration. Washout periods were established for the glycemic-lowering drugs proportional to their half-lives both in the presurgical and the postsurgical periods: 24 hours for basal insulins (glargine, detemir and NPH) or oral antidiabetic drugs, 6 hours for regular human insulin and 3 hours for rapid acting analogs (glulisin, lispro and aspart).

Patients were followed until surgery had taken place and they were contacted again by telephone to organize the second blood test extraction. The same procedure described previously was conducted between 4-8 weeks after surgery to quantify glucose insulin and C-peptide. These data were compared to the presurgical results. No changes in antidiabetic medications were made during this period.

C-peptide values before and after surgery were compared to a series of parameters to check for any possible significant relationship. These comprised years of evolution of T2DM, BMI, HbA1c, fasting glycemia, HOMA-B (homeostasis model assessment) and diabetic complications. Besides, a subgroup of patients were specifically studied to detect differences in pancreatic reserve: patients treated with insulin *vs.* patients not receiving insulin.

Taking advantage of the fasting plasma insulin and glucose determination, HOMA-B for insulin secretion was calculated as an indirect measurement of beta cell function according to the formula:

[20 x basal insulin (mUI/mL)] / [fasting glucose -3.5].[22]

The HOMA-B value has shown a good correlation with the pancreatic beta cell area in humans in an investigation based on histological samples conducted by Fujita *et al.*[23]

The study was approved by the Ethics Committee of University Hospital Dr. Negrin following the Helsinki Declaration and according to the Spanish law relative to observational studies (Ministerial Order SAS/3470/2009). All patients signed an informed consent form after accepting to be included in the study.

### *C-peptide measurement*

Blood samples were processed by the IMMULITE analyzer (Siemens), which quantifies C-peptide in serum, heparinized plasma or urine.[24] This is a solid phase, chemoluminiscent, immunometric assay. The solid phase consists of a ball covered with murine anti-C-peptide monoclonal antibody, whilst the liquid phase is a combination of bovine intestine alkaline phosphatase and murine anti-C-peptide monoclonal antibody conjugated in a tamponated solution.

Both the patient's sample and the reactant are incubated together with the ball during 30 minutes. Along this time, C-peptide from the sample forms sandwich complexes with the murine anti-C-peptide monoclonal antibody from the ball and the conjugated enzyme. Later, the non-bound patient's sample and conjugated enzyme are cleared by centrifugated wash. Finally, the chemoluminiscent substrate is added to the unit containing the ball and a signal is generated proportionally to the amount of bound enzyme.

An incubation cycle of 30 minutes is performed and the first determination is obtained after 42 minutes. C-peptide concentration results are expressed as nanograms per milliliter (ng/mL). The assays variation coefficient is 1.9-3%.

### *Statistical analysis*

The "R" software was used to carry out the statistical analysis of the data, version 3.0.0.[25] For the descriptive analysis of the quantitative variables we chose averages, median values and standard deviations (SD).

Shapiro-Wilk Test was performed when variables followed a normal distribution. Related samples were studied with the paired t-test. To compare independent samples, Wilcoxon Test was used when normality hypothesis was rejected.

We considered differences to be statistically significant when error probability (P value) was less than 0.05.

## Results

Initially, 72 patients were identified as candidates for the study: 22 refused to participate, 7 were excluded because surgery had not been performed before the end of data collection and 1 refused to undergo the postsurgical blood test. In the end, 42 patients were included in the analysis. Basal characteristics of the patients and ASA (American Society of Anesthesiologists) physical status classification are described in Table I. Most frequent diagnosis for surgery and surgical procedures are detailed in Tables II, III.

About half of the patients were treated with only one oral antidiabetic agent, receiving the other half two or more drugs: 47.6% were receiving metformin in monotherapy, 4.76% received repaglinide in monotherapy and 47.4%

TABLE I.—*General characteristics of the patients expressed by mean value (standard deviation).*

| | |
|---|---|
| N. | 42 |
| Age (average) | 62.16 years (6.25) |
| Sex: male/female | 47.6/52.4% |
| Time of evolution of DM | 7.33 years (7.23) |
| HbA1c (%) | 7.00% (1.47) |
| BMI (kg/m$^2$) | 29.13 (5.36) |
| Familiar history of DM (%) | 38.1% (16) |
| Treated with insulin | 21% (9) |
| Cardiovascular risk factors | |
| Hypertension | 73.8% (31) |
| Dyslipidemia | 61.9% (26) |
| Smokers | 16.7% (7) |
| Ischemic cardiopathy | 16.7%(7) |
| Stroke | 2.4% |
| Microvascular complications | |
| Diabetic retinopathy | 7.1% |
| Diabetic nephropathy | 11.1% |
| ASA | |
| 2 | 64.3% |
| 3 | 35.7% |

ASA physical status classifies patients in six different categories (from ASA 1 -normal health patient- to ASA 6 -brain-dead patient-), according to each patient's sickness before performing surgery.
ASA: American Society of Anesthesiologists; DM: diabetes mellitus; HbA1c: glycated hemoglobin.

TABLE II.—*Presurgical diagnosis of patients.*

| Diagnosis | N. | % |
|---|---|---|
| Multinodular goiter | 2 | 4.8 |
| Breast cancer | 4 | 9.5 |
| Prostate cancer | 3 | 7.1 |
| Cholelitiasis | 9 | 21.4 |
| Cholecystitis | 1 | 2.4 |
| Lumbar stenosis | 2 | 4.8 |
| Carotid stenosis | 3 | 7.1 |
| Uretral stenosis | 2 | 4.8 |
| Cervical disk herniation | 1 | 2.4 |
| Lumbar disk herniation | 7 | 16.7 |
| Hiperparathyroidism | 1 | 2.4 |
| Prostate benign hypertrophy | 1 | 2.4 |
| Biliar pancreatitis | 1 | 2.4 |
| Breast cancer sequels | 5 | 11.9 |
| Total | 42 | 100 |

had metformin associated to other. Detailed data about antidiabetic treatment is shown in Table IV. With regards to insulin usage, 9 patients (21.4%) were receiving insulin either on basal or premixed insulin regimens. Of them, 55.5% had a long acting analog (glargine or detemir), 33.3% received intermediate acting insulin (NPH-neutral protamine Hagedorn-) and 11.1% were on premixed insulin. None of them was on a basal-bolus regimen.

TABLE III.—*Surgical proceedings.*

| Type of surgery | N. | % |
|---|---|---|
| Suprapubic prostatic adenomectomy | 1 | 2.4 |
| Laparoscopic cholecystectomy | 11 | 26.2 |
| Cervical diskectomy | 1 | 2.4 |
| Lumbar diskectomy | 7 | 16.7 |
| Lumbar laminectomy | 2 | 4.8 |
| Thyroid lobectomy | 1 | 2.4 |
| Radical mastectomy | 1 | 2.4 |
| Parathyroidectomy | 1 | 2.4 |
| Uretral plastia | 2 | 4.8 |
| Laparoscopic radical prostatectomy | 3 | 7.1 |
| Implantation of prothesis and expansors | 2 | 4.8 |
| Reconstruction with pediculated flap | 3 | 7.1 |
| Carotid endarterectomy | 3 | 7.1 |
| Total thyroidectomy | 1 | 2.4 |
| Tumorectomy + sentinel adenopathy biopsy | 3 | 7.1 |
| Total | 42 | 100 |

TABLE IV.—*Type of oral antidiabetic treatment.*

| | N. (%) |
|---|---|
| Monotherapy | |
| Metformin | 20 (47.6) |
| Repaglinide | 1 (2.38) |
| Combination therapy (all with metformin) | |
| iDPP4 | 7 (16.6) |
| iDDP4 and SU | 5 (11.9) |
| iDPP4 and repaglinide | 3 (7.14) |
| SU | 4 (9.52) |
| Repaglinide | 2 (4.7) |

No patients received pioglitazone. No patients on montherapy with iDDP4 or SU.
iDPP4: inhibitor of dypeptidyl peptidase 4; SU: sulphonylureas.

Among the non-antidiabetic drugs, the two most frequently used were antihypertensives (73.8%) and statins (52.3%). Antagonists of the receptor of angiotensin type 2 (ARA2) were the most widely observed antihypertensive (42.85% of the total). Antiaggregation with acetylsalicylic acid was seen in 42.85% of the patients too.

Basal C-peptide before surgery was 2.97 ng/mL (0.1-6.62, SD 1.54), and presurgical C-peptide after glucagon was 5.53 ng/mL (0.1-18.4, SD 3.13), being this increment of 2.56 ng/mL (0-12.26, SD 1.99) statistically significant (P<0.001). In the postoperative period, basal C-peptide was 3.12 ng/mL (0.1-11.3, SD 1.95) and after glucagon it raised up to 5.67 ng/mL (0.1-18.9, SD 3.86). This mean difference of 2.55 ng/mL (0-11.11, SD 2.25) was also sig-

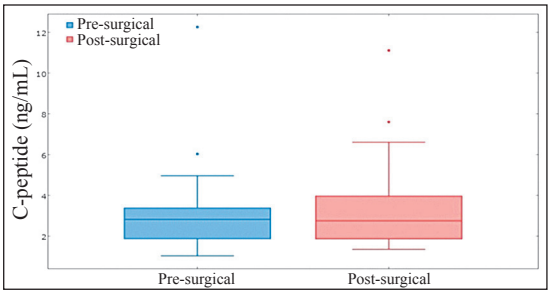


Figure 1.—C-peptide data.

nificant (P<0.001). Patients with higher basal C-peptide showed bigger increments after glucagon stimulation both in the presurgical and the postsurgical setting (P<0.001).

Pancreatic reserve stayed the same or increased in 69.04% of the patients and diminished in 30.95%, albeit these data did not reach statistical significance. The main parameter of pancreatic beta cell function, the difference between C-peptide increments after glucagon measured before surgery compared to the postoperative period, was not significant (2.56 ng/mL *vs.* 2.55 ng/mL, mean difference -0.02). Data shown in Figure 1.

Presurgical HOMA-B mean value was 89.62 (median 68.4, SD 80.22), while postsurgical HOMA-B mean value was 82.64 (median 66.1, SD 75.64). There was a difference of 6.98 units between both measurements, but it did not reach significance (P=0.41). Regarding patients previously treated with insulin, 88% of them maintained their pancreatic reserve without significant changes, opposed to 11% of subjects where it diminished. Hence our deduction that diabetic patients already on an insulin-based treatment do not suffer a pancreatic beta cell deterioration after surgery, according to the Fisher exact test (P=0.03).

## Discussion

In general, our patients were overweight mature adults (age 60-65 years) who had suffered from T2DM for several years. We can state that they are quite similar to patients commonly treated in Primary Care services. Usually, patients attending the hospital are older, with a much longer T2DM time of evolution, receiving several oral antidiabetic drugs and/or complex insulin therapies and presenting different complications. The fact that the patients included had such a good glycemic control (mean HbA1c 7.0%) supports the notion that they were quite comparable to the Primary Care setting, with milder T2DM reflecting larger pancreatic beta cell reserve.

As can be inferred from the results we obtained, the pancreatic beta reserve of patients with T2DM was not affected a month after the non-urgent surgery. The direct measurement of pancreatic function by dynamic assessment with glucagon did not change, nor did we find alterations in the indirect calculation of insulin secretion using the HOMA-B. None of these parameters reached statistical significance.

Perhaps the physical and psychological stress to which these subjects were exposed were not enough to elicitate an important change in their previous glycemic metabolism. Surgical aggression accompanied by its subsequent inflammatory state and the modification in hormonal secretion might not be strong enough to induce a relevant alteration in the beta cell population of patients with T2DM. There is the chance that a short lasting hyperglycemia occurred after surgery but it did not persist as long as a month later, when we performed the tests to look for differences. As we did not analyze changes in insulin doses after surgery, subtle modifications might have been undetected. Different surgeries could imply different outcomes, but the number of patients enrolled did not permit us to differentiate among surgical procedures. However, we think the main aim of the study − assessing the effect of surgery on a patient with type 2 diabetes − gives us a fairly approximate idea of what happens to surgical diabetic patients.

Other consideration may be the inclusion of patients with cancer in our study (four surgical procedures for breast cancer and five breast reconstructions after mastectomy), as cancer implies a more intense inflammatory state. Only one of these four patients had disseminated disease. Thus, we think that the remaining three patients undergoing cancer surgery with local disease and the five breast reconstruc-

tions in recurrence-free women did not affect the results of the whole sample.

With these data, therefore, we can say that the non-urgent surgical procedures included in our study are safe for patients with short lasting, properly controlled T2DM, from the point of view of glucose metabolism assessed by pancreatic insulin secretion.[25]

However, there is a series of considerations that must be taken into account when interpreting these results. Performing the second test a month after surgery may be not long enough to detect actual differences, and a glucagon test a few months after surgery could give different results. Using studies in bariatric surgery as an example, where modified secretion of incretins can be proved after longer periods, a delayed effect on glucose could happen that has not been detected due to this study's design. It would be interesting to perform the same measurements several months after surgery and look for changes in HbA1c after 6-12 months. Pancreatic beta cells might be capable of coping with a precocious increased demand of insulin secretion after a few weeks after the surgical aggression, but this could affect overall pancreatic reserve and only be evident in the long term. The appearance of complications according to the state of preservation of insulin secretion could also be worth studying, as these events take a longer time to take place, as UKPDS trials showed.[26]

Early alterations in glucose metabolism could happen in other surgical interventions not included in our investigation. However, we believe that the surgical procedures included in this study are representative of the usual surgical population of a tertiary level hospital. Other surgeries where the digestive system is not manipulated have been excluded to avoid situations that would add confusion: those involving remarkable alterations of food intake (persistent ileus, postsurgical abdominal pain, proceedings with risk of anastomotic leakage, etc.) with possible subsequent loss of weight and altered insulin resistance; and techniques with important modifications of the bowel transit which may produce changes in endogenous incretin secretion, as has been observed in bariatric surgery.

Another different and appealing clinical situation would be having results from patients with poorly controlled T2DM, as the subjects analyzed had in general a very good glycemic control, because this could mean they are more capable of withstanding any kind of metabolic aggression. Diabetic patients with higher HbA1c values have a smaller beta cell reserve, and stress might produce different outcomes.

Conclusions can be also applied to patients treated with insulin, despite having been considered a subgroup of people with lower initial pancreatic beta cell reserve expressed by a partial or total failure of oral antidiabetics. However, results are equal to the rest of our population. This theoretical difference in beta cell function was not observed (basal C-peptide levels similar to those of the main sample), so quantitatively the effects of surgery were the same for this subgroup.

Our results are concordant with previous known facts about insulin secretion capacity throughout the evolution of T2DM: subjects with a better basal pancreatic beta cell function respond in a stronger way to stimulation (in this case, higher basal C-peptide values had higher C-peptide levels after glucagon). As the population we studied had a good glycemic control, this effect of glucagon on insulin and C-peptide secretion was quite predictable.

In the publications we have previously referred to, lower C-peptide values were observed in patients previously on insulin, similarly to what happened in our own study, although it did not meet statistical significance. These data support the scientific evidence already favoring insulin treatment in the advanced stages of T2DM, albeit could not be confirmed in our investigation.

According to our results, we can consider that patients with T2DM undergoing different non-urgent surgical procedures will not be likely to suffer a significant decrease of their insulin secretion a month after the operation.

## Conclusions

We can consider non-urgent surgical procedures safe from the point of view of the pres-

ervation of the pancreatic reserve in patients with T2DM. A sharp deterioration of metabolic control is not expectable in the short term for these patients, which represent a large proportion of the population undergoing surgery in modern hospitals.

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