Biliopancreatic Diversion with Duodenal Switch in Patients with Type 2 Diabetes mellitus: Is the Chance of Complete Remission Dependent on Therapy and Duration of Insulin Treatment?

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Keywords

Biliopancreatic diversion with duodenal switch · BPD-DS · Type 2 diabetes mellitus · Complete remission · Insulin

Summary

Background: Rapid resolution of type 2 diabetes mellitus (T2DM) is a common feature after intestinal bypass surgery bypassing the duodenum and parts of the jejunum. However, the parameters determining the individual chance of remission are imprecisely defined. **Methods:** Biliopancreatic diversion with duodenal switch and sleeve gastrectomy (BPD-DS) was performed in $n = 86$ patients with T2DM (mean age 50 years, range 26–68, 51 females; BMI 47 kg/m², range 26–71). The patients were retrospectively divided into 4 groups according to the treatment modality and the duration of insulin treatment preoperatively: $n = 18$ patients were treated with oral antidiabetic drugs only (group 1); $n = 32$, $n = 24$, and $n = 12$ patients were treated with insulin for less than 5 years, for 5–10 years, and for more than 10 years (groups 2, 3, and 4), respectively. **Results:** At discharge from hospital, all patients of groups 1 and 2 were free of insulin usage, 30% and 75% of the patients of groups 3 and 4 used up to 48 units of insulin per day (mean 24, $n = 16$). After 1 year, only 4 patients of group 4 permanently required small amounts of insulin (mean 17 units per day) to keep blood glucose below 200 mg/dl. These 4 patients had been using insulin preoperatively for 13, 15, 22, and 25 years. In 3 of these 4 patients, fasting C-peptide was measured and found to be low (<1.2 ng/ml). The rate of complete remission of diabetes for the whole study population was 91%. **Conclusion:** BPD-DS reliably causes

rapid and complete remission of T2DM in all patients on oral antidiabetic drugs and in patients with insulin treatment for less than 5 years. In patients with insulin treatment longer than 5 or 10 years, complete remission rates decline to 88 and 66%, respectively. A low C-peptide preoperatively might be a specific adverse prognostic parameter for the chance of diabetes remission.

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive chronic metabolic disease eventually leading to microvascular and macrovascular complications [1]. Despite of best state-of-the-art therapy, diabetes is insufficiently controlled in most patients by conventional therapeutic means [2]. As a consequence, the mortality rate of patients with T2DM is increased by a factor of more than 4 compared to a control population of patients without diabetes mellitus [3]. There is a novel therapeutic option in the armamentarium of diabetes therapy: metabolic intestinal bypass procedures, causing remission of T2DM in 80–95% of the patients [4]. Intestinal procedures that bypass the duodenum and the proximal or entire jejunum induce a long-lasting improvement or remission of T2DM [5–7]. The antidiabetic effect usually appears within a few days after surgery long before a significant weight reduction occurs [5]. Thus weight reduction that in itself causes improvement of T2DM either by diet [8] or by restrictive surgical procedures [9] cannot be made responsible for the rapid improvement seen after intestinal bypass procedures [10]. Insulin sen-

sitivity recovers 3–7 days following intestinal bypass surgery [5, 11, 12] whereas it is unchanged after restrictive procedures [13]. Remission is defined as achieving glycemia below the diabetic range in the absence of active pharmacologic or surgical therapy, a complete remission is a return to ‘normal’ measures of glucose metabolism ($\text{HbA}_{1\text{C}} < 6\%$, fasting glucose $< 100 \text{ mg/dl}$ of at least 1-year duration) [14]. Biliopancreatic diversion according to Scopinaro (BPD) [6] and biliopancreatic diversion with duodenal switch (BPD-DS) [7] have been shown to be the most effective operations concerning remission rate of T2DM. However, only few studies exist which demonstrate the effect of the operation on long-standing and mostly insulin-requiring T2DM. It is not known whether the remission rate in BPD-DS is dependent on therapy and duration of insulin-treatment as has been demonstrated for Roux-en-Y gastric bypass [15]. The aim of the present study is to analyze our data on patients with T2DM, 80% of whom were using insulin, with respect to freedom of insulin treatment, time course of $\text{HbA}_{1\text{C}}$, and complete remission rate.

Patients and Methods

The patient population consisted of 84 consecutively operated on patients with T2DM. All patients underwent a BPD-DS. The primary indication for surgery was T2DM in nearly all cases. Since the primary indication for BPD-DS was based on T2DM and not on morbid obesity, some of the patients’ body mass index (BMI) was lower than 35 kg/m^2 (see accompanying paper of Frenken and Cho). The decision for surgery was made in collaboration with a multidisciplinary team including a diabetologist. All patients were well informed about the risks and benefits of the procedures, and about the necessity of lifelong surveillance and dietary supplementation with vitamins, micronutrients, calcium, on occasion iron, and proteins. They usually participated in a support group before surgery. In $n = 41$ of our insulin-requiring patient population, values of preoperative fasting C-peptide were available. Autoantibodies were determined to rule out misdiagnosed type 1 diabetes or latent autoimmune diabetes of adulthood (LADA). The present study analyses data collected prospectively in our database.

Table 2. Patient characteristics

	Total ($n = 86$)	Group 1 ($n = 18$)	Group 2 ($n = 32$)	Group 3 ($n = 24$)	Group 4 ($n = 12$)
Mean age, years (range)	50 (26–68)	50 (28–63)	47 (26–68)	51 (38–64)	58 (44–67)
Gender (females/males), n	51/35	10/8	17/15	16/8	8/4
Mean BMI, kg/m^2 (range)	47 (26–71)	46 (26–61)	47 (32–71)	46 (30–63)	47 (35–69)

Table 3. Diabetes characteristics before surgery

	Total ($n = 86$)	Group 1 ($n = 18$)	Group 2 ($n = 32$)	Group 3 ($n = 24$)	Group 4 ($n = 12$)
Mean duration of diabetes treatment, years (range)	9.8 (0.3–40)	7.0 (0.3–40)	5.3 (1–15)	12.5 (7–27)	20.0 (11–30)
Mean duration of insulin treatment, years (range)		–	2.5 (0.3–4)	7.5 (5–10)	15.2 (11–25)
Mean insulin usage/day, units (range)			87 (20–250)	160 (60–500)	159 (69–300)
Mean $\text{HbA}_{1\text{C}}$, % (range)	9.4 (6.0–14.3)	9.1 (6.0–13.5)	9.5 (6.0–14.3)	9.5 (6.8–12.3)	9.5 (6.9–11.8)

Surgical Technique

BPD-DS was performed as an open procedure either by a median incision or by a transverse upper abdominal incision with a median extension to the xyphoid (Mercedes star incision). A gastric sleeve resection was performed along a 44 French bougie. Motility of the antrum was preserved by starting the resection 6–8 cm above the pylorus. The duodenum was transected approximately 4–5 cm distal to the pylorus. The small bowel was usually transected 250 cm proximal to the ileocolic valve, but at 300 cm if the total length of the small bowel exceeded 600 cm. A duodenoileostomy was performed and the oral end of the transected small bowel anastomosed to the ileum approximately 100 cm proximal to the ileocolic valve, thus creating a common channel of 100 cm. A cholecystectomy and an appendectomy were routinely performed simultaneously.

Follow-Up

All patients were routinely re-examined 3, 6, and 12 months after surgery in our cooperating diabetes department (Diabeteszentrum Rheinland in Haan) and once every year further on in our own department.

Grouping of the Patients

All patients were grouped into 1 of 4 groups according to therapy and duration of insulin treatment (table 1).

Results

Table 2 shows the baseline characteristics of the patients. Data are shown for the total patient population ($n = 86$) and for each of the 4 groups. Diabetes characteristics are shown in table 3. It is evident from these data that 79% of all patients

Table 1. Grouping of the patients according to therapy (oral antidiabetic drugs versus insulin) and to the duration of insulin treatment

Group	Therapy	Patients, n
1	oral antidiabetic drugs only	18
2	insulin therapy < 5 years	32
3	insulin therapy 5–10 years	24
4	insulin therapy > 10 years	12

Fig. 1. Percentage of patients using insulin at different time points. All 4 groups are shown. Demonstrated is the usage of insulin preoperatively, at discharge from hospital, and 6 months and 1 year after BPD-DS. Insulin usage is dependent on preoperative therapy and duration of insulin treatment (OAD = oral antidiabetic drug, Ins = insulin treatment).

were using insulin. The mean HbA_{1c} level preoperatively was similar in all 4 groups demonstrating insufficient control of glucose metabolism independent of duration of T2DM or therapy of T2DM.

To prevent glucotoxic effects of glucose in the postoperative course, rigorous efforts were undertaken to keep plasma glucose levels lower than 200 mg/dl. Insulin was given whenever either fasting glucose or preprandial or postprandial glucose levels were elevated above 200 mg/dl. Because of the very rapid increase in insulin sensitivity after BPD-DS [12], usually only small amounts of insulin were necessary. Short-acting insulin was usually given 3 times a day before meals. Insulin therapy was tapered after discharge from hospital whenever possible.

The percentage of patients using insulin preoperatively and postoperatively is shown in figure 1 for each of the 4 groups. None of the 18 patients who did not use insulin preoperatively needed insulin at discharge or later on. However, 1 patient is being continuously treated with metformin 850 mg once a day by his general practitioner in spite of normalized glycemic values. Also, none of the 32 patients who used insulin for less than 5 years preoperatively was in need of insulin at discharge from hospital or later on. However, in group 3 (patients who used insulin for 5–10 years), 7 patients (30%) were discharged with small amounts of insulin (mean 18 units, range 12–30). One year after surgery, all patients of this group were also off insulin. However, 3 of the patients exhibited an elevated HbA_{1c} level (up to 8%), but all of them denied taking insulin again. Most interestingly, 9 of the 12 patients of group 4 using insulin for more than 10 years preoperatively were in need of insulin in small amounts (mean 29 units, range 12–48) at discharge. In some of these patients, insulin could be tapered with improvement of metabolic state and weight loss, but 4 of the patients in this group had to use insulin also after 1 and 2

Fig. 2. Time course of HbA_{1c} preoperatively and 3 months, 6 months, 1 year, and 2 years after BPD-DS. Shown are mean values, for reasons of clarity the range (maximum–minimum) is given only for preoperative HbA_{1c} values and the values after 2 years.

years and further on (follow-up 4 years). These 4 patients had used insulin preoperatively for 13, 15, 22, and 25 years. One and 2 years after surgery, they used on average 17 units insulin a day (range 12–22).

The time course of the level of HbA_{1c} after surgery is demonstrated in figure 2. In all 4 groups, the preoperatively elevated HbA_{1c} values declined, but the pace of decline was different in the 4 groups. The mean HbA_{1c} level normalized within 3 months after surgery in the patients treated with oral antidiabetic drugs (OAD) only or treated with insulin for less than 5 years. In patients treated with insulin for 5–10 or more than 10 years, mean HbA_{1c} levels normalized only after 6 months and after 2 years, respectively. After 2 years, only 3 patients of group 3 showed elevated HbA_{1c} values, and 4 patients of group 4 used insulin to maintain good glycemic control.

We measured C-peptide in our most recently operated on 41 patients who were using insulin (out of 68 patients using insulin). All 32 patients with a C-peptide > 1.5 ng/ml experienced a complete remission of diabetes regardless of duration of insulin treatment (mean duration of insulin treatment 6 years, range 0.5–25). The mean HbA_{1c} level of these 32 patients after 1 year was 5.2% (range 3.7–5.9). Nine patients had a low C-peptide between 0.6 and 1.4 ng/ml. Only 5 of these patients experienced a complete remission. In 4 of the 9 patients, we observed a failure to achieve remission. In 3 of 4 patients of group 4 who did not achieve a remission of T2DM, C-peptide values were found to be lower than 1.2 ng/ml.

Complete remission rate for all our 86 patients was 91%. In group 2, 1 patient used metformin in spite of normalized glycemic values; in group 3, 3 patients had elevated HbA_{1c} values in the absence of medical therapy; and in group 4, 4 patients used insulin in small amounts to keep glycemic values in the normal range. Thus, complete remission rate was 100, 97, 88, and 66% in groups 1, 2, 3, and 4, respectively.

Discussion

We analyzed the data of 86 patients with T2DM undergoing BPD-DS. The primary indication for surgery was T2DM in all cases. Most of our patients had advanced disease, approximately 80% of the patients were using insulin. From the present analysis some important findings can be obtained:

Remission Rates – Dependence on Therapy and Duration of Insulin Use

First, we observed a normalization of glycated hemoglobin in most of our patients with T2DM after BPD-DS. The decline of the HbA_{1c} level to normal values appeared to be independent of therapy (oral antidiabetic drugs versus insulin) or duration of insulin treatment as long as the preoperative fasting C-peptide was not lower than 1.5 ng/ml. We found low C-peptide levels only in patients with a long history of insulin-requiring T2DM. Low C-peptide levels in patients with long-standing insulin therapy are associated with an irreversible dysfunction of the beta cells of the pancreas [16]. Thus if insulin production of the beta cells of the pancreas is still sufficiently high to match endogenous needs, BPD-DS reliably induces complete remission of T2DM. As a consequence, all 32 patients in our series with fasting C-peptide of > 1.5 ng/ml and also all 50 patients treated with oral antidiabetic drugs only, even for 4 decades, or treated with insulin for less than 5 years, experienced a decline in glycated hemoglobin to normal values within 1 year after surgery.

Our findings are in contrast to the effects of Roux-en-Y gastric bypass on T2DM. Schauer et al. [15] analyzed 240 patients with morbid obesity and type 2 diabetes or prediabetes undergoing a gastric bypass procedure. A total of 191 patients were re-examined 6–54 months after the operation. Out of these patients, 14 patients had prediabetes before the operation, 32 patients had diabetes controlled by lifestyle intervention and diet, 93 patients used OAD, and 52 patients were using insulin. Remission was observed in 97% of the diet controlled patients, 87% of the patients using OAD, and 63% of insulin using patients. Patients with a history of diabetes for 5 or less years, for 6–10 years, and for more than 10 years experienced remission of T2DM in 95, 75, and 54%, respectively. Thus, there was a clear dependence on therapy and duration of the disease. Most differently from our data, some patients with not far advanced T2DM did not experience remission of T2DM after Roux-en-Y gastric bypass. This might be a consequence of different pathophysiological modes of actions of the different procedures. Whereas after BPD or BPD-DS, the rapid disappearance of insulin resistance [11, 12] may be the most important factor for resolution of T2DM, an increased stimulation of beta cells after Roux-en-Y gastric bypass caused by increased postprandial secretion of gastrointestinal hormones like GLP-1 and PYY might be the initial and crucial factor of rapid remission of T2DM in this kind of metabolic intestinal bypass surgery [10].

High remission rates of 100 and 96% have been reported after standard BPD [17, 18] and after BPD-DS [19]. Scopinaro et al. [18] reported on a 100% remission rate in morbidly obese patients with T2DM including 108 patients treated with OAD and 32 patients treated with insulin. However, the authors neither stated the duration of diabetes treatment nor whether the remission is complete according to the stringent definitions defined by a consensus group of the American Diabetes Association. Marceau et al. [19] report a remission rate of 96%. However, the authors did not mention how many patients were using insulin preoperatively but only described that 2 of 3 patients with failure of remission were insulin using preoperatively and used OAD after operation. Our own data presented in this paper are consistent with the assumption of an astonishing high remission rate after BPD, even in far advanced diabetes disease. 79% of our patients were suffering from insulin requiring T2DM, the mean duration of manifest diabetes was nearly 10 years. Nevertheless we observed an overall rate of complete remission of 91% according to the current definitions [14]. Thus, the remission rates of T2DM after BPD/BPD-DS seem to be consistently higher than the remission rates reported in large series after Roux-en-Y gastric bypass [5, 15]. This has also been confirmed by the large meta-analysis of Buchwald et al. [4] on surgery in obese patients with diabetes which included more than 135,000 patients. These authors found a remission rate of 80.3% after Roux-en-Y gastric bypass and of 95.1% after BPD/BPD-DS. To our best knowledge, no analysis has been published yet regarding the rate of diabetes remission in relation to treatment modality, duration of T2DM, and duration of insulin treatment in T2DM patients after BPD or BPD-DS except of our own preliminary studies [20].

Rate of Normalization of Blood Glucose

Second, in every patient who was treated with OAD only or treated with insulin for less than 5 years, we found a normalization of blood glucose levels in the absence of pharmacologic therapy within a few days. However, the longer the insulin therapy was before surgery (above the threshold of 5 years), the higher the chance of failure of immediate freedom of insulin therapy shortly after surgery. Is the need for insulin in the early postoperative stage also dependent on the BMI or age of the patients? The mean BMI values of all 4 groups were actually very similar, also the weight loss after BPD-DS was similar in all groups (not shown) precluding a primary role of BMI or weight loss on the rate of normalization of blood glucose after surgery. As expected, the age of the patients increased with duration of T2DM. Nevertheless, the rapid normalization of glycemic metabolism did not seem to be a result of age: In all 4 groups, the age of the patients varied widely. If age were of major importance for the rapid versus slowed normalization of glycemic metabolism, one would expect a slowed improvement of blood glucose levels in some older patients of group 1 and a rapid improvement in younger patients of group 4, which

was not observed. Hence, the chance of rapid normalization of blood glucose levels within few days after surgery is directly dependent on the treatment modality of T2DM and the duration of insulin treatment but not on BMI or age of the patients.

About Insulin Resistance

Third, the maximal amount of insulin needed at discharge from hospital to achieve near normal blood glucose levels was only 48 units insulin per day (mean 24 units). These very low amounts of insulin even in the most insulin-resistant and most insulin-deficient T2DM patients is particularly remarkable, since the mean insulin usage preoperatively amounted to approximately 125 units per day and in some individuals up to 500 units per day. Despite such huge amounts of insulin required preoperatively and despite the usually long-lasting specific diabetes care by a diabetologist, T2DM in most of the patients was under poor control as evidenced by levels of glycated hemoglobin of up to more than 14%.

The mean insulin production of a healthy human adds up to approximately 40 units per day [21]. This amount parallels the amount of insulin requirement of an insulin-deficient patient with type 1 diabetes or a patient suffering from pancreoprivic diabetes, in both cases without insulin resistance, to avoid hyperglycemic situations. Thus the maximal needed amount of insulin in the postoperative setting after BPD-DS is similar to basal insulin production in healthy subjects or basal insulin requirement in an insulin-deficient patient. This suggests that if insulin is needed in BPD patients postoperatively, it is necessary to compensate for partial endogenous secretion failure and not to surmount insulin resistance.

A hallmark of T2DM is insulin resistance [16]. Possibly due to glucotoxic effects [22] in patients with long-standing insulin resistance, a progressive secretion failure of the beta cells of the pancreas evolves [23, 24]. However, insulin resistance can disappear immediately after metabolic intestinal bypass surgery. A rapid recovery of insulin sensitivity in obese patients with T2DM has been shown after standard BPD [18] and after BPD with duodenal switch [12]. Frenken and Cho [12] determined insulin sensitivity (defined as the reciprocal of insulin resistance) in 27 morbidly obese patients with manifest T2DM undergoing a BPD-DS using the homeostasis model assessment of insulin resistance (HOMA-IR) [25]. HOMA-IR is a surrogate index for insulin sensitivity/resistance; a value of ≤ 1 represents a normal insulin sensitivity in a healthy human. Due to the lack of a standardized insulin assay, it is not possible to define universal cut-off points for insulin resistance [26]. However, HOMA-IR values of > 2.5 are considered to indicate insulin resistance, HOMA-IR values of > 5 are common in patients with T2DM. The mean HOMA-IR decreased from 14.3 (range 2.1–72.2) preoperatively to 3.6 (range 1.1–8.5), 1.9 (range 0.4–4.9), 1.9 (0.2–4.5), and 1.9 (range 1.0–2.4) 3, 7, 14, and 21 days after surgery. Thus, a recovery of insulin sensitivity was found within 1 week after BPD-DS, and after

3 weeks every single patient had lost his insulin resistance. It has been demonstrated that the recovery of insulin sensitivity after BPD-DS was independent of the severity and duration of T2DM, and also independent of BMI and age. Also, in 3 patients in need of insulin at discharge from hospital, insulin sensitivity recovered [12].

Rate of Normalization of HbA_{1c}

Fourth, the time course of normalization of glycated hemoglobin is strongly dependent on therapy and duration of T2DM. This dependency is very similar to the dependency of the time course of rapid glycemic control on therapy and duration of T2DM. It seems likely that 2 distinct mechanisms work on improvement of T2DM after BPD-DS: on the one hand there are patients with less advanced disease treated with OAD only or treated with insulin for less than 5 years. In these patients glucose levels and HbA_{1c} levels normalize very rapidly within few days after surgery and they no longer require any pharmacologic therapy or specific antidiabetic diet. This phenomenon is most likely due to a very rapid and complete loss of insulin resistance. These patients do not show clinical signs of beta cell dysfunction. On the other hand, in patients with more advanced disease (duration of insulin usage of more than 5–10 years), a second component of diabetes improvement is unveiled which acts slowly. The more advanced the diabetes and the longer the duration of insulin usage is, the more likely is a clinical manifestation of progressive secretion failure. Even after rapid normalization of insulin sensitivity, endogenous insulin production does not meet the requirements, so these patients need exogenous insulin in the early phase after surgery. However, in a good portion of these patients, a steady slow improvement occurs, and in most of these patients insulin treatment can be discontinued. This mechanism resembles the improvement of glucose metabolism after restrictive surgical procedures in which an improvement of glucose metabolism parallels the weight loss [9, 27]. However, it is not clear whether the slow component is due to the weight loss (as in restrictive surgery) or due to a slow weight-independent recovery of the secretory function of the beta cells.

Conclusions

BPD-DS causes complete remission of T2DM in the majority of patients. We found a complete remission rate of 91% in our patients with predominantly far advanced disease. The chance of achieving complete remission after BPD-DS does not depend on the severity and duration of the disease as long as the secretory function of the beta cells of the pancreas is clinically sufficient as evidenced by a C-peptide level of > 1.5 ng/ml. Two mechanisms seem to be at work in diabetes improvement. First, there is a rapid weight- and age-independent action inducing rapid normalization of glycemia and HbA_{1c} probably caused by a rapid disappearance of insulin resist-

ance. Second, there seems to be a distinct action which is working slowly. This mechanism might be directly correlated to weight loss or might indicate a steady improvement of beta cell function. BPD and BPD-DS are the most effective operations for T2DM. Since the chance of complete remission of T2DM is dependent on sufficient beta cell function, surgery for T2DM should not be delayed until irreversible deterioration of beta cells occurs. Thus, surgery should best be considered before 5 years' duration of insulin treatment. However,

even in the few patients with far advanced T2DM and very long-standing insulin treatment, who do not achieve complete remission, an impressive improvement of T2DM is observed. Even in these patients surgery may be worthwhile.

Disclosure Statement

The authors declare no conflicts of interest.

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