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Long-Term Control of Type 2 Diabetes Mellitus and the Other Major Components of the Metabolic Syndrome after Biliopancreatic Diversion in Patients with BMI <35 kg/m^2

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Background: Bariatric operations are the most powerful means of curing type 2 diabetes mellitus (T2D) and the other major components of the metabolic syndrome. Despite the very frequent occurrence of metabolic disturbances in patients with BMI from 30 to 35, there is a general reluctance to operate on these patients, as their disease is considered less severe.

Methods: 7 T2D obese patients with mean BMI <35 underwent BPD between 1976 and 1996 at the Azienda Ospedaliera Universitaria San Martino of Genoa, Italy. Mean age was 49 years, mean body weight 91 kg, and mean waist circumference 115 (M) and 98 (F) cm. The mean follow-up was 13 (10-18) years. All 7 patients had abnormally high values of serum triglyceride, serum cholesterol, and arterial pressure.

Results: In all patients, serum glucose was normalized at 1, 2, and 3 years. In 5 patients, a slight increase of serum glucose above 125 mg/dl was observed at or around 5 years, the values being maintained at all subsequent times, with no one value higher than 160 mg ever being recorded. The other 2 patients showed full resolution of diabetes at all follow-up times. Both serum cholesterol and triglyceride values fell to normal 1 year after BPD, and remained within the normal range in all 7 patients during the entire follow-up observation. Arterial pressure normalized in 6 cases and was improved in I case. No patient had excessive weight loss at any postoperative time.

Conclusions: T2D patients with BMI <35 have very severe metabolic disturbances. Surgical therapy for these patients is warranted, and it should be performed as soon as possible, before the rapid evolution of the pattern leads them to a point where even the most effective metabolic surgery operation could be insufficient to yield complete and permanent control of their diabetes.

Key words: Obesity, obesity surgery, biliopancreatic diversion, type 2 diabetes, metabolic syndrome

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Introduction

Bariatric operations result in improvement or disappearance of metabolic complications of obese patients.[1-3] While this effect is simply consequent to weight reduction after pure gastric restriction procedures, specific actions have been demonstrated for gastric bypass (GBP) and biliopancreatic diversion (BPD). In particular, GBP is followed by an ~80% resolution of type 2 diabetes mellitus (T2D),[4,5] whereas nearly 100% cure of all the major components of the metabolic syndrome was observed after BPD.[6] Both these operations show their effects immediately after surgery, and they are maintained at long term, independently of the weight changes.

However, although an even greater occurrence of metabolic complications, and thus increased cardiovascular disease risk, was observed in patients with BMI between 30 and 35 in comparison with higher levels,[7,8] there is general reluctance to use bariatric surgery in the treatment of these patients.

Because BPD is unanimously recognized as the most effective operation for obesity metabolic complications, the results of BPD in patients with BMI <35 are of great interest.

Materials and Methods

The charts of all patients submitted to BPD from 1976 to 1996 were reviewed (after 1996, when with the Prague IFSO Statement[9] the indications for bariatric surgery were definitively established, no patient with BMI <35 was operated on). Out of 2,212 patients (671 males) reviewed, 102 (20 males) had preoperative BMI <35 kg/m^2. Seven of them had T2D (serum glucose >125 mg/dl) at the time of operation, and they were evaluated for serum glucose, triglycerides, cholesterol, and arterial pressure preoperatively and at different postoperative times. All patients had completed the routine 3-year follow-up visits. Subsequently, four patients have regularly sent to us their laboratory data, as all of our operated patients are asked to do, after the third year, for life. Two of them, whose recent data were lacking, were called by phone and sent us their examination results. One patient, operated on 15 years before, was not found. However, his data were available regularly until the 9th postoperative year.

There were five males and two females. Mean serum glucose was 253 (131 to 400) mg/dl, mean age was 49 (39 to 60) years, mean body weight 91 (81 to 139) kg, with a mean BMI 33.4 (32.0 to 34.6) kg/m^2, mean waist circumference 115 (111 to 121) cm for men and 98 (92 and 104) cm for women. The mean follow-up was 13 (10 to 18) years. In five patients, diagnosis of T2D had been made 4 to 10 years before surgery, and all of them were in therapy with oral hypoglycemics, while in 2 patients unsuspected hyperglycemia was found at BPD, in both cases mild but in the diabetic range.

All seven patients had abnormally high values of serum triglyceride (mean 312 mg/dl, range 145 to 995), serum cholesterol (mean 272 mg/dl, range 205 to 406) and arterial pressure (maximal normal values 140 and 85 mmHg for systolic and diastolic, respectively).

Results

After BPD, changes of body weight and of serum glucose levels of the seven subjects are reported in Figure 1, Figure 2, and in Table 1, where also serum triglyceride and cholesterol values are shown.

In all patients, serum glucose was normalized at 1, 2 and 3 years. In the five patients with preoperative history of T2D, a slight increase in serum glucose >125 mg/dl was observed at or around 5 years. These slightly abnormally high values were maintained in all the five patients at all subsequent times, with no one value higher than 160 mg/dl ever recorded. The two patients with slightly abnormal values unexpectedly found at operation showed full resolution of T2D at all follow-up times. All seven preoperatively-diabetic patients remained on totally free diet and with no medication throughout the entire follow-up.

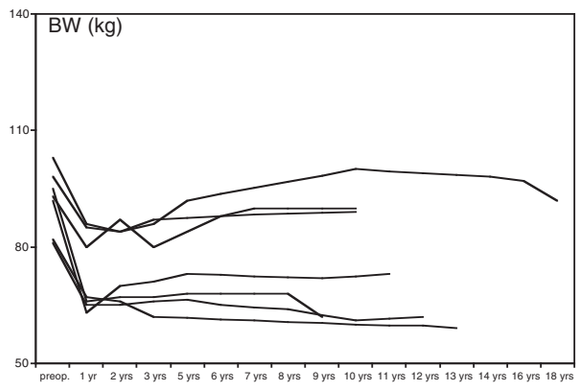

Figure 1. Changes of body weight in seven type 2 diabetic patients with BMI <35 undergoing BPD.

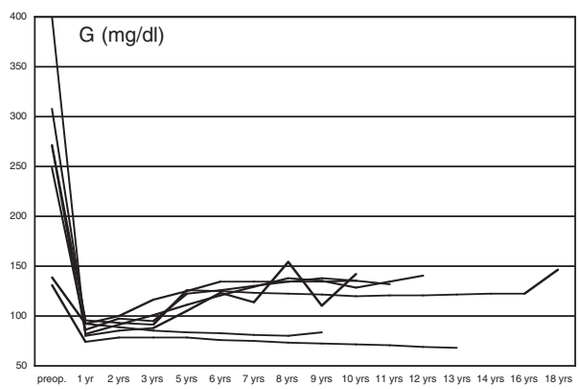

Figure 2. Changes of serum glucose concentrations in seven type 2 diabetic patients with BMI <35 undergoing BPD.

Table 1. Type 2 diabetic patients with BMI <35 kg/m^2 undergoing BPD. Body weight (BW, kg), BMI (kg/m^2), and serum glucose (G, mg/dl), triglycerides (TG, mg/dl), and cholesterol (Chol, mg/dl) concentrations prior to BPD and at different postoperative times. OA: oral antidiabetic agents. Abnormal data in bold type

		preop	1 yr	2 yrs	3 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs	11 yrs	12 yrs	13 yrs	14 yrs	16 yrs	18 yrs
C.P. (1988)	BW	103	86	84	86	92					100				98	97	92
male, 39 yrs	BMI	**32.1**	26.8	26.2	26.8	28.7					**31.2**				**30.6**		28.7
O.A. for 4 years	G	**272**	96	93	91	**126**					120				122	122	**146**
	TG	**995**	**285**	**237**	130	77									130		131
	Chol	**406**	140	130	120	103									110		114
M.N. (1991)	BW	95	66	67	67	68			68	62							
male, 60 yrs	BMI	**34.5**	23.4	23.7	23.7	24.1			24.1	22.0							
diagnosis at BPD	G	**139**	92	89	85	84			80	84							
	TG	**255**	122	75	76	74			80	76							
	Chol	**281**	148	166	112	102			133	141							
F.L. (1993)	BW	82	67	66	62									59			
female, 49 yrs	BMI	**34.6**	28.3	27.8	26.1									24.9			
diagnosis at BPD	G	**131**	74	78	78									68			
	TG	**165**	121	124	96									105			
	Chol	**205**	121	127	138									125			
P.C. (1994)																	
female, 59 yrs	BW	81	65	65	66		65		64		61		62				
O.A. for 4 years	BMI	**33.3**	26.7	26.7	27.1		26.7		25.9		25.1		25.4				
	G	**271**	82	91			121		**138**		**128**		**140**				
	TG	**173**	**179**	128			131		115		117		120				
	Chol	**253**	**212**	160			174		107		124		125				
A.S. (1995)	BW	92	63	70	71	73				72		73					
male, 45 yrs	BMI	**34.6**	23.7	26.3	26.7	27.5				27.1		27.5					
O.A. for 4 years	G	**248**	86	97	95	122				**138**		**132**					
	TG	**211**	112	**226**	**150**	**141**				135		125					
	Chol	**301**	107	140	135	168				140		115					
S.A. (1996)	BW	93	80	87	80		88				89						
male, 59 yrs	BMI	**32.6**	28.0	**30.5**	28.0		**30.8**				**31.2**						
O.A. for 7 years	G	**308**	92	100	116		**134**				**135**						
	TG	**145**	120	104	115		138				112						
	Chol	**226**	115	125	107		117				106						
D.A. (1996)	BW	98		84	87		88	90		90	90						
male, 49 yrs	BMI	**32.0**		27.4	28.7			29.8			29.8						
O.A. for 10 years	G	**400**		85	88		123	114	**154**	110	**142**						
	TG	**237**		115	101		80	110	101	93	97						
	Chol	**233**		120	98		110	150	116	118	110						

Both serum cholesterol and triglyceride values fell to normal 1 year after BPD, and remained within the normal range in all seven patients during the entire follow-up observation (Table 1).

Arterial pressure normalized at 1 year in four cases, at 2 years in two additional operated patients, and remained normal in all the six cases. In one case, arterial hypertension improved but failed to disappear, and continued to require medical therapy.

No patient at any postoperative time had excessive weight loss (Table 1). The average weight loss was from 92 to 75 kg, maintained indefinitely as is usual after BPD. In particular, the four patients with the higher BMI values experienced the higher weight loss, while the three with the lower BMI showed minimal weight reduction from their initial BMI value of ~32 (Figure 3). No relation was observed in any case between body weight and serum glucose changes (Figure 4).

Discussion

Some interesting considerations can be made regarding the age, the male/female ratio, and the frequency of T2D in our population of 102 patients with BMI <35 and of the seven out of that group with T2D. While the mean age of the 102 patients was similar to that of our general population (37 years), the age of the seven diabetic patients was, expectedly, considerably higher (49 years). The M/F ratio was 1/4 in the patients with BMI <35 when compared to the M/F ratio of 1/2 in our general population, and this can easily be explained when considering that in that range of overweight, women are more likely to be motivated for surgery for cosmetic reasons. The relative scarcity of men also partly explains the low frequency of T2D in the BMI <35 population (7%), when compared to that of our general population of operated patients (20%); this contrasts with the findings of the Swedish School, which observed that the risk of metabolic complications of obesity, and thus of cardiovascular disease, is higher when the waist/hip ratio is greater and the BMI is smaller.[7,8] The low percentage can also be explained by the fact that, until recently, obese patients requested surgery with only weight reduction in mind, and thus were almost totally unaware of the metabolic results of bariatric operations. It is then understandable why a moderately obese but severely diabetic patient was as a first choice mainly attracted by the internist who was treating his/her diabetes, who, even knowing the results, would have never suggested an invasive therapy such as surgery for treatment of obesity, and even less of diabetes.

Contrary to what happened in the group of 102 patients with BMI <35, the M/F ratio was 5/2 in the seven T2M patients, which is in full agreement with the universally accepted concept that central (android) obesity is so strictly associated with all the components of the metabolic syndrome that it is considered as one of them. As a matter of fact, mean waist circumference in the five men was 115 cm and in the two women 98 cm, the mean waist-to-hip ratio being 1.07 and 0.90, respectively.

Angrisani et al[10] in 2004 reported a restrospective analysis of 225 patients with BMI <35 submitted to adjustable gastric banding for obesity between 1996 and 2002. There were 4 (1.8%) diabetic patients in that population and T2D had resolved in all of them 1 year after the operation, when the excess weight percent loss was 52.5 in the whole group.

Cossu et al,[11] later in 2004, described the results of BPD with stomach preservation and duodenal switch on 24 patients with one or more of the components of the metabolic syndrome and "BMI <40 kg/m^2". Their mean preoperative BMI was 36.2, ranging from 24.7 to 46.7, but the authors do not specify how many patients had a BMI <35. Mean follow-up was 4 years. Seventeen patients had T2D, 20 had hypercholesterolemia, while the number of patients with hypertriglyceridemia was not reported.

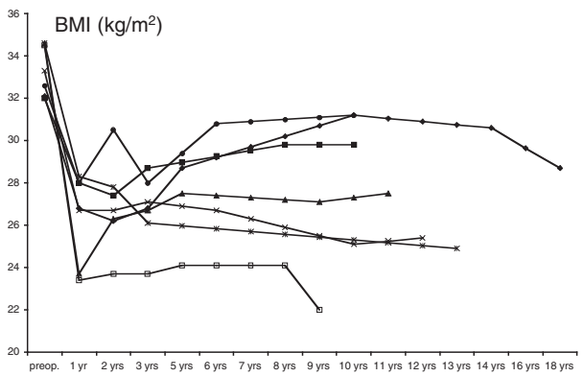

Figure 3. Changes of BMI in seven type 2 diabetic patients with BMI <35 undergoing BPD.

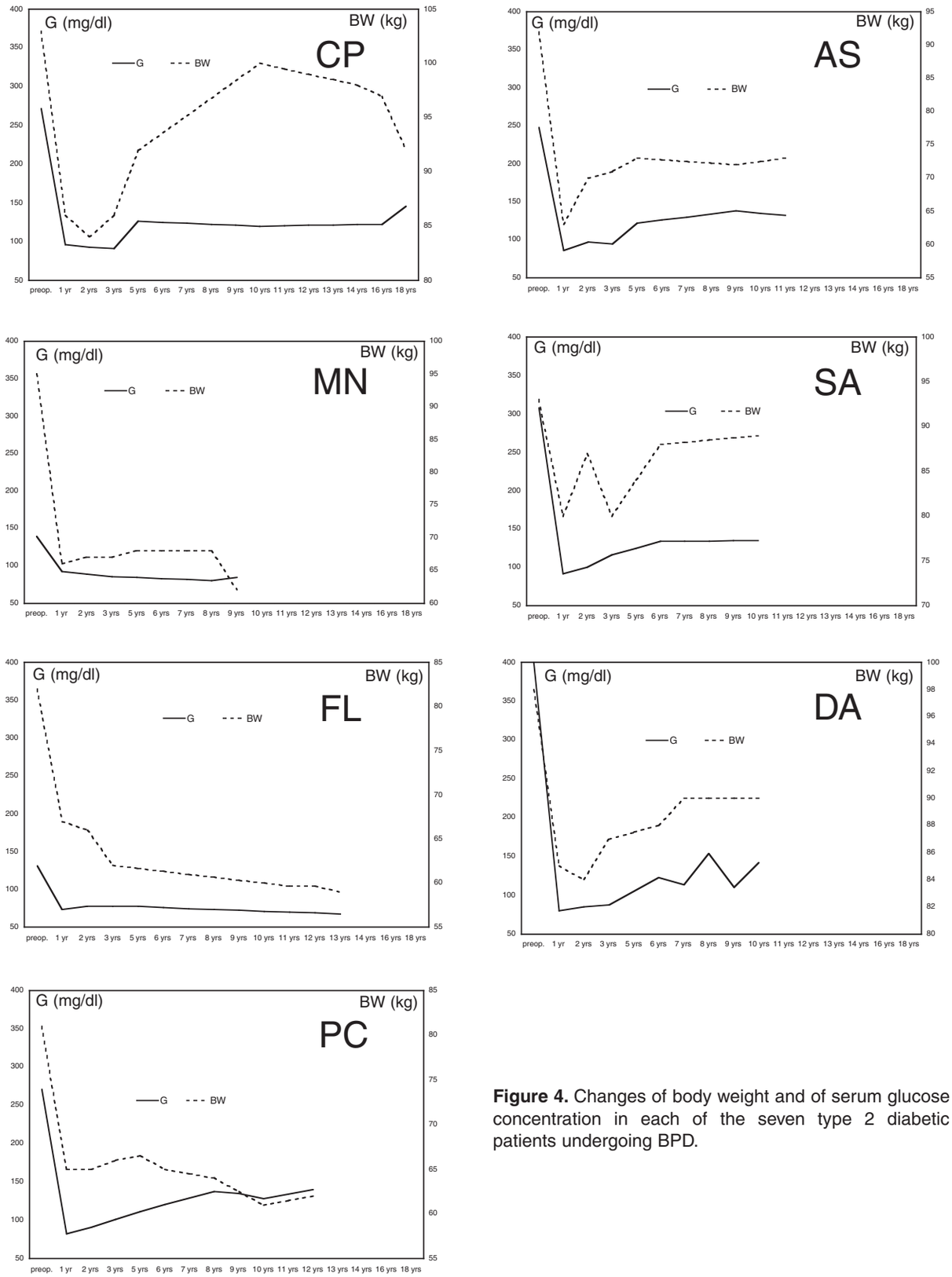

Figure 4. Changes of body weight and of serum glucose concentration in each of the seven type 2 diabetic patients undergoing BPD.

Two of the 17 diabetic patients had no improvement of T2D, so they were converted to standard BPD, two were also converted to a Scopinaro procedure because of recurrent stomal ulcer (total incidence 29.1%), and three other patients continued to necessitate oral antidiabetic treatment. The other 10 previously diabetic patients improved, but their mean fasting serum glucose level remained between 100 and 110. Serum cholesterol and triglycerides were permanently normalized in all cases.

Very recently, Cohen et al[12] reported a series of 37 obese patients with BMI <35 who underwent gastric bypass and were followed for 6-48 months. All patients had T2D, hypertension and "lipid disorder". All of them were free of these complications after GBP, with the only exception being one patient who still had mild hypertension. However, despite the authors regret that the requirement of having "severe and uncontrollable obesity-related co-morbidities" had limited the size of their patient population, this series appears to be constituted by individuals with only mild metabolic derangements. In fact, mean age was only 34 years, mean fasting glucose (with diabetes being defined by serum glucose ≥120) only 146 mg/dl, mean serum cholesterol (maximum normal level being considered 240) only 252 mg/dl, and mean serum triglycerides (maximum normal value 170) only 204 mg/dl. Indeed, it is quite unusual that mildly obese patients with T2D have such mild lipid disturbances. Again, very unexpectedly, the male/female ratio in that series was 1/3, this standing for a very low centrality of obesity, which is also reflected in the mean waist circumference (104 cm for men with maximum normal 102, and 90 cm for women with maximum normal 88).

What appears most impressive in our small series of T2D patients with low BMI is the fact that they apparently behave quite differently than the much bigger series of T2D obese patients with BMI >35 reported by us elsewhere.[6] In fact, in the population of more severely obese patients, serum glucose concentration normalized within the first postoperative year and remained in the normal range until the tenth year in nearly all cases. Differently, in the present series five out of seven patients showed serum glucose that normalized at 1 year and remained normal for only 3 to 4 years. Around the fifth postoperative year, serum glucose rose slightly above the diabetic threshold and remained in a range between 110 and 150 mg/dl during the entire subsequent follow-up period, ie. up to >10 years.

Let us remember that T2D results from the combination of two adverse events, ie. insulin resistance and impaired β-cell function. Obesity causes insulin resistance, thus determining increased insulin production aimed at maintaining normoglycemia. This in turn increases insulin resistance, which closes the vicious circle known as "downregulation". If the β-cell is a healthy one, a long time may elapse before that vicious circle leads to a level of insulin resistance such as to cause the insulin production to be insufficient to maintain normoglycemia, with diabetes development. If, on the contrary, mainly due to genetic factors, the β-cell function is impaired, diabetes may appear with low levels of insulin resistance, and thus a low degree of obesity. Therefore, a T2D appearing with a low degree obesity, as happened in our series, means a severely impaired β-cell function,[13] with consequent expectation of a diabetes rapidly evolving into a clinically severe one.

While five of our patients, namely those with a minimum 4-year diabetes history, evidently were in that bad situation, with a highly deteriorated metabolic condition already apparent, the two who were diagnosed at BPD with mild hyperglycemia were in an onset condition, which, with the increase in body weight, would have certainly evolved towards a severe diabetes, although in that specific phase they were relatively easily curable. These last two patients appear rather similar to patients in Cohen's series,[12] and this could explain his good results with an operation which is undoubtedly less effective than BPD.

BPD acts on T2D through different mechanisms. Two of them have been identified with the duodenal bypass with the consequent gut hormone changes,[14] and the minimal fat absorption causing the myocellular fat depletion with ensuing reversal of insulin resistance.[15,16] However, other additional, still unknown control mechanisms may be active. When this powerful action constellation meets a T2D with sufficiently preserved β-cell function, it results in complete indefinite control of the metabolic disturbance, with permanent normoglycemia. If, on the contrary, the β-cell function is already severely impaired, as apparently happened in the five patients in our small series with slightly unsatisfactory outcome, BPD actions again take good control of the metabolic alterations; however, after a period of com-

plete control with normoglycemia, they result in an apparently indefinite period where the control is still very active, but cannot maintain normoglycemia.

This is not different from what happened in our larger series of diabetic patients with BMI >35, with two patients where serum glucose level never normalized but was permanently reduced into a range between 110 and 160 mg/dl, and in three patients who had the same course as the five in this study, showing an initial serum glucose normalization followed by a slight increase of glycemia, which permantly remained in the same range.[6] In both series, this happened on a totally free diet and without any medication.

The seriousness of the metabolic derangement of all patients in our series is also witnessed by the presence of hypercholesterolemia, hypertriglyceridemia and arterial hypertension, ie. all the major components of the metabolic syndrome. As usually happens, BPD resulted in total and permanent cure of all these conditions.

The individual graphs in Figure 3 show that, as already pointed out elsewhere, there was no relation between changes in serum glucose and changes in body weight after BPD. On the average, the seven patients lost little weight (92 to 75 kg), simply because they had little weight to lose. Since BPD has a maximum energy absorption capacity,[17,18] which obviously corresponds to the weight of stabilization, the more the preoperative weight approaches that weight of stabilization, the less will be the weight loss. This simple reasoning should reassure those surgeons and internists who, due to the wrong idea that any bariatric operation inevitably causes weight loss, fear an excessive weight reduction for the patients with low BMI. In reality, the intestinal energy absorption capacity is very different for fat and starch. Certainly an individual undergoing BPD at the weight of stabilization should not lose weight because the energy that he/she ate before the operation equals the energy that he/she will absorb postoperatively. However, it is most probable that that individual usually eats more fat than what he/she will be able to absorb, and less starch than what will be his/her starch absorption capacity. In conclusion, a lean subject submitted to BPD, in order to maintain his/her body weight, will have to increase the amount of starch eaten at least up to the starch absorption threshold, in order to compensate for the reduction of fat absorption.

This is what three of our operated patients did, essentially maintaining their body weight (from a mean of 98 to a mean of 93 kg) (Figure 1). The other four patients evidently did not make this compensation, and thus had a sizeable weight reduction (85 to 64 kg). It is noteworthy, and again reassuring, that none of these patients ever became underweight. It should also be noted, that, compensated or not, the minimal fat absorption consequent to BPD is the main factor responsible for the excellent metabolic results obtained in the five T2D patients with severely impaired β-cell function and all the other major components of the metabolic syndrome, and the operation would be highly beneficial for any patient submitted to BPD, for any reason and with any starting body weight.

There is considerable emotion around the issue of bariatric operations on metabolic patients with BMI <35. The majority of obesity professionals are highly reluctant to do surgery with BMI <35, which is explained keeping in mind that, being used to thinking in terms of body weight, they consider the disease of the population with BMI <35 to be mild. On the contrary, this study unequivocally demonstrates that these patients are the most severe ones from the metabolic point of view. Nevertheless, standard BPD proved effective in obtaining in these difficult patients, besides permanent normalization of all the other major components of the metabolic syndrome, stable control of their T2D at long and very long term.

In conclusion, type 2 diabetic patients with BMI <35 have very severe metabolic disturbances. Surgical therapy for these patients is warranted, and it should be performed as soon as possible, before the rapid evolution of the pattern leads them to a point where even the most effective metabolic surgical operation could be insufficient to yield complete and permanent control of their diabetes.

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