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ORIGINAL CONTRIBUTIONS

Serum Leptin and Adiponectin Concentration in Type 2 Diabetes Patients in the Short and Long Term Following Biliopancreatic Diversion

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Abstract
Background A deranged adipokine system is implicated in obesity and in type 2 diabetes mellitus (T2DM), and the lack of remission of T2DM after bariatric surgery could be also accounted for by the postoperative persistence of this condition.
Methods Thirty T2DM patients undergoing biliopancreatic diversion (BPD) with a wide range of baseline body mass index (BMI) were evaluated prior to and at 1 and 5 years following BPD. Besides the usual clinical evaluations, acute insulin response (AIR) to intravenous glucose load as a parameter of insulin secretion and the serum leptin and adiponectin concentration were measured throughout the follow-up period in all patients.
Results A long-term T2DM remission was observed in 21 patients (70 %). Serum leptin level reduced at the first year and remained substantially unchanged at a long term in both the remitter and non-remitter patients, while following the operation, a progressive significant increase of serum adiponectin level was observed only in remitter patients (from 9.2 to 12.3 μg/mL at 1 year and to 15.18 μg/mL at 5 years in the remitters and from 8.8 to 8.75 μg/mL at 1 year and to 11.8 μg/mL at 5 years in the non-remitters). Serum leptin mean values were positively associated with the BMI ones both prior to and following BPD ($p < 0.005$), while serum adiponectin values were positively related ($p < 0.04$) to the postoperative AIR data.
Conclusions The improvement of the pattern of cytokine production, as evidenced by postoperative rise in serum adiponectin concentration, might play a role in T2DM remission after bariatric surgery.

Keywords Acute insulin response · Adiponectin · Bariatric surgery · Leptin · Type 2 diabetes

Bariatric surgery has proven efficacy in both long-term weight loss and glycemic control in severely obese patients with type 2 diabetes [1–3]: besides a stable weight loss, bariatric surgery can produce a complete and persistent type 2 diabetes mellitus (T2DM) remission and it is currently recognized by the International Diabetes Federation [4] and American Diabetes Association [5] as a viable treatment option for obese adults with T2DM. The metabolic outcome seems to be related to the extent of weight reduction, the best results being observed following the operations that induce a consistent loss of body mass: after adjustable gastric banding, only 20–30 % of type 2 diabetes patients succeed in normalizing or reducing fasting serum glucose level, while after laparoscopic Roux-en-Y gastric bypass (LRYGBP) and biliopancreatic diversion (BPD), a successful metabolic outcome after the operation is observed in 60–70 and 85–95 % of the operated subjects, respectively [6–8]. However, since in the severely obese patients the reduction toward normalization of fasting blood glucose after RYGBP and BPD is usually observed before a clinical meaningful weight loss, a specific effect due the operation on diabetes remission has been hypothesized. The new functional–anatomic conditions of the upper gastrointestinal tract due to the operation cause a rearrangement of enterohormonal secretion

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patterns that would be responsible of the metabolic changes observed after the operation. The bypass of duodeno-jejunal juice from the food transit and the early contact of non-digested foods with more distal intestinal loops increase the secretion of GIP and GLP-1, incretins that have gastrointestinal and insulinotropic effects [9–11]. Furthermore, the passage of partially digested aliments through the distal ileum causes an increase of secretion in PYY, a distal enterohormone that specifically stimulates satiety [12]. Furthermore, the rerouting of the upper gastrointestinal tract after BPD and long-limb RYGBP causes changes in gut microbiome ecology and in enterohepatic circulation, with an increase of bowel bile acid content: experimental studies have suggested that this leads to revert the hepatic and global pro-inflammation status, consequently improving glucose and lipid metabolism [13, 14]. For BPD, the fat intestinal malabsorption due to the operation causes a significant lipid deprivation from the fist postoperative days and then a marked decrease of the intracellular lipid storage that sharply increases muscle insulin sensitivity [15]. In spite of the marked weight loss and the powerful specific effects of the operation, the T2DM remission does not take place in all the BPD and RYGBP patients and diabetes relapse may develop at a long term. Recently, review studies and meta-analysis have demonstrated that, regardless of the type of operation and diabetes duration, the lower the baseline degree of obesity, the higher is the rate on unsatisfactory postoperative metabolic outcomes [16, 17].

Serum adiponectin levels are decreased in obese people compared to normal individuals, while pro-inflammatory adipokines such as tumor necrosis factor-α, interleukin-6, leptin, and monocyte chemoattractant protein are elevated, and this is associated with an increased insulin resistance or the appearance of overt T2DM [18–20]. In uncomplicated severely obese patients, at a short term after surgically obtained weight loss, a marked rise in serum adiponectin was observed, accompanied by a trend of a decrease of pro-inflammatory TNF-α and MCP-1, suggesting a more equilibrate balance of adipose tissue-derived cytokines and then an improvement in metabolic conditions [21–24].

The aim of this study was to investigate the role of the adipokine system in the T2DM non-remission after bariatric surgery.

Since in the T2DM overweight and mildly obese patients undergoing bariatric surgery the rate of negative metabolic outcome was higher than that in their severely obese counterpart [16, 17], most of the T2DM patients considered for this study have a preoperative body mass index (BMI) lower than 35 kg/m^2.

Material and Methods

A group of 30 (21 males and 9 females) T2DM patients aging from 37 to 69 years (mean 55) undergoing BPD specifically for T2DM treatment with a preoperative T2DM mean duration of 9.3 years (from 3 to 17 years) were investigated. Diagnosis of T2DM was set according to the American Diabetes Association criteria [5]; all patients were treated with antidiabetic drugs and 10 patients received insulin therapy. All patients underwent the standard type of BPD. The operation was described in detail elsewhere [25]. The sample comprehends T2DM patients with BMI values lower than 35 kg/m^2 who participated in a pilot study aimed to evaluate the effects of BPD in T2DM patients with overweight or mild obesity [26]. Peri- and postoperative treatment was the usual for BPD at our institution.

For this investigation, only the preoperative findings and those obtained at 1 and 5 years following the operation were considered. Furthermore, only data directly regarding glucose metabolism and beta cell function are discussed. Data of all patients were available before BPD and both at 1 and 5 years after the operation.

Body weight (BW) was determined to the nearest 0.1 kg and height at the nearest 0.5 cm. Fasting blood glucose (FBG, mg/dL) and glycated hemoglobin (HbA1c, %) concentrations were measured with a routine analyzer while insulin concentration by a commercial enzymatic method (Randox, Crumlin, UK) and sandwich immunoradiometric assay (Immunotech, Prague, Czech Republic). Serum leptin and adiponectin concentrations were determined by radioimmunoassay (DRG Diagnostics, Marburg, Germany). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated [27].

Insulin secretion was assessed as the acute insulin response (AIR) to an intravenous glucose bolus (glucose 35 g over 2 min) before surgery and at 1 and 5 years after BPD. The intravenous glucose tolerance test (IVGTT) was performed at 8:30–9:00 a.m. after a 12-h overnight fast; blood samples were collected 10 min before, immediately before the glucose injection, and 2, 3, 5, and 10 min afterward. AIR quantitative data were obtained as the difference of the mean insulin concentration at 2, 3, 5, and 10 min after glucose injection minus the mean insulin concentration at 10 and 0 min before IVGTT.

Informed consent was obtained from all the individual participants included in the study.

T2DM remission was defined when an HbA1c value was steadily equal to or lower than 6.4 % on free diet and with no antidiabetic therapy. Since the study was carried out on very long-term data and the sample size was relatively small, the subjects considered both as complete and partial remitters were included in the remission group [28].

Data is given as mean ± SD. Since data has no normal distribution, statistics were performed with non-parametric tests: longitudinal comparisons were analyzed with the Wilcoxon signed-rank test and groups were compared by the Mann–Whitney *U* test; the relationships between data were evaluated by Spearman's rho analysis. Calculation was carried out with Statview 2.3 (Cary, NC).

Table 1 Type 2 diabetes patients undergoing biliopancreatic diversion (BPD): anthropometric, biochemical, and functional data (mean ± SD) prior to 1 and 5 years following BPD

	Prior to BPD	At 1 year from BPD	At 5 years from BPD
Cases (*n*)	30	30	30
BW (kg)	99.1 ± 22.5	76.1 ± 12.7*	75.8 ± 16.4*
BMI (kg/m^2)	36.3 ± 8.4	27.7 ± 3.9	28.3 ± 4.4*
%TWL (%)		21.7 ± 10.7	22.3 ± 16.5*
FBG (mg/dL)	203 ± 58	127 ± 53*	122 ± 37*
HbA1c (%)	8.7 ± 1.3	5.7 ± 1.3*	6.1 ± 1.4*
HOMA-IR	8.1 ± 6.3	1.7 ± 1.2	2.6 ± 1.9
AIR[a] (μU/mL)	1.76 ± 3.49	8.9 ± 16.62	11.2 ± 20.83$^{\neq}$

BW body weight, *BMI* body mass index, *%TWL* percent of total weight lost, *FBG* fasting blood glucose, *HbA1c* glycated hemoglobin, *HOMA-IR* homeostatic model of assessment of insulin resistance, *AIR* acute insulin response

[a] To intravenous glucose load

*$p < 0.001$, vs. prior to BPD; $^{\neq}p < 0.05$, prior to BPD

Results

At the fist postoperative year, the T2DM was remitted in 21 patients (70 % of the cases) and the remission rate decreased at the fifth post-BPD year in 18 patients (60 % of the cases).

As expected, in comparison with the preoperative data, at the first postoperative year, a marked reduction of BW and BMI mean level was observed, and values were substantially maintained at 5 years. With respect to the findings obtained before BPD, at the first postoperative year, the FBG and HbA1c mean values were significantly reduced and remained nearly unchanged at 5 years. Likewise, the insulin resistance, as assessed by HOMA, data sharply reduced at 1 year following BPD and subsequently remained within physiological limits until the fifth year after the operation (Table 1).

Finally, the mean AIR values showed a marked, though not significant, increase at the first postoperative year and, at the fifth year following BPD, the values were substantially unchanged (Table 1).

After the operation, the serum leptin mean values decreased at the first postoperative year and remained substantially stable throughout the follow-up period (Table 2). On the contrary, at the first post-BPD year, the serum adiponectin mean levels were nearly similar to baseline, while at the fifth year, a not statistically significant increase was found (Table 2). The serum leptin concentration throughout the postoperative period was substantially similar in all the operated patients. By contrast, in the subjects who experienced a long-term T2DM remission, the serum adiponectin concentration was markedly increased at the first post-BPD year, with a further significant rise at the fifth year, while in the patients with a negative postoperative metabolic outcome, the serum adiponectin mean values remained substantially unchanged throughout the follow-up period (Table 2).

Serum leptin values were positively associated with BMI values prior to BPD (rho = 0.709, $p < 0.005$) and at the first postoperative year (rho = 0.654, $p < 0.001$) and at the fifth postoperative year (rho = 0.551, $p < 0.003$) (Fig. 1). On the contrary, the serum adiponectin concentration was completely

Table 2 Type 2 diabetes patients undergoing biliopancreatic diversion (BPD): serum adiponectin and leptin concentration (mean ± SD) prior to 1 and 5 years following BPD in all cases and in patients with and without T2DM remission at the fifth postoperative year

	Prior to BPD	At 1 year from BPD	At 5 years from BPD
All cases (*n*)	30	30	30
Adiponectin (μg/mL)	9.2 ± 6.1	10.7 ± 6.7	14.6 ± 7.7
Leptin (ng/mL)	18.2 ± 16.1	12.6 ± 12.4 §	10.4 ± 11.1 *
T2DM remission at 5 years			
All cases (*n*)	18	18	18
Adiponectin (μg/mL)	9.3 ± 6.4	12.3 ± 8.3 §	15.18 ± 7.6 §
Leptin (ng/mL)	23.07 ± 18.56	12.6 ± 12.4 §	13.9 ± 13.1 §
No T2DM remission at 5 years			
All cases (*n*)	12	12	12
Adiponectin (μg/mL)	8.8 ± 5.55	8.73 ± 3.06	11.8 ± 7.7
Leptin (ng/mL)	9.9 ± 7.53	6.1 ± 3.5 §	4.9 ± 2.4 §

§ $p < 0.01$, vs. prior to BPD; *$p < 0.0001$, vs. prior to BPD

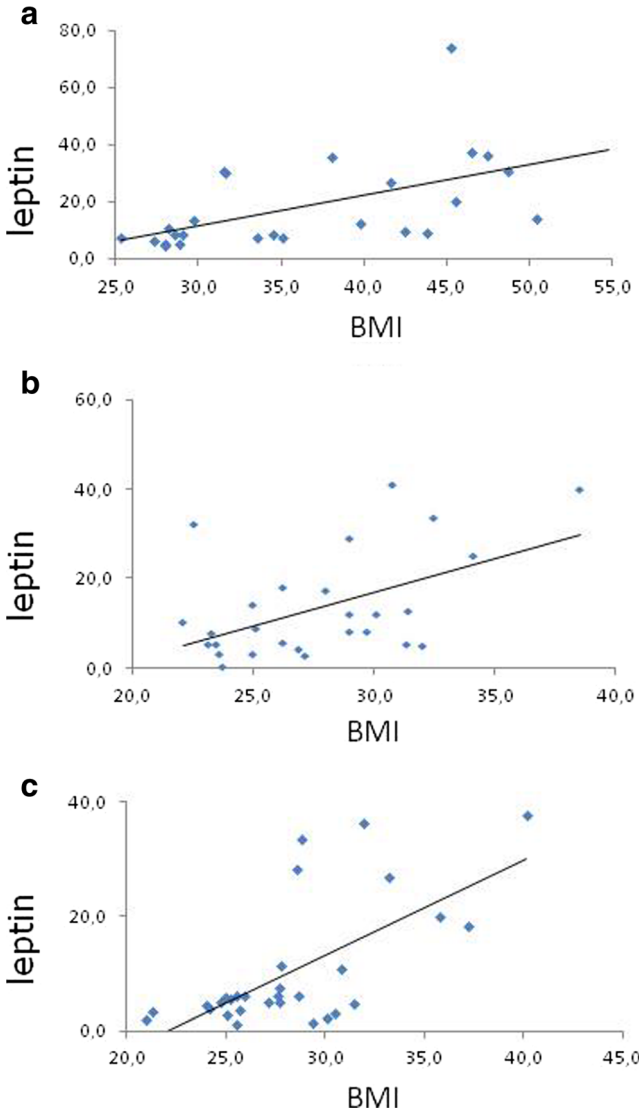

Fig. 1 T2DM patient undergoing biliopancreatic diversion. Association (with trend) between the serum leptin concentration and BMI value prior to BPD (**a**, rho = 0.709, $p < 0.005$) and at the first postoperative year (**b**, rho = 0.654, $p < 0.001$) and at the fifth postoperative year (**c**, rho = 0.551, $p < 0.003$)

unrelated to the baseline BMI values, while a positive association between serum adiponectin levels and AIR values was observed both at 1 year (rho = 0.467, $p < 0.012$) and 5 years (rho = 0.297, $p < 0.04$) following BPD (Fig. 2).

Discussion

Over the last two decades, adipose tissue depots have been established as highly active endocrine and metabolically important organs that modulate energy expenditure and glucose homeostasis, being responsible for the secretion of an array of signaling molecules, termed adipokines, that promote the communication between organs, including the brain, liver, muscle, immune system, and adipose tissue itself [19, 20, 29]. The dysregulation of the adipokine system causes a low-degree chronic inflammation status that is implicated in obesity, type 2 diabetes, and cardiovascular disease [18, 29]. Adipose tissue secretes various pro- and anti-inflammatory adipokines both to regulate feeding behavior and energy expenditure and to modulate inflammation and insulin resistance; the obesity-induced insulin resistance and type 2 diabetes may result, at least partly, from an imbalance in the expression of pro- and anti-inflammatory adipokines [18–20, 30]. Adiponectin is an anti-inflammatory hormone that has been shown to reduce atherosclerosis and increase insulin sensitivity through increasing fatty acid oxidation and inhibition of hepatic glucose production [18, 19, 31]. Furthermore, as an anti-inflammatory agent, adiponectin inhibits the tumor necrosis factor-α activation and stimulation, promotes the differentiation of macrophages to remove apoptotic cells, and modulates the T cell and the anti-inflammatory function of natural killer cells [19]. Serum leptin level is elevated in overweight and obese patients, the values being positively related to the body fat size [32]. A development of a true leptin resistance status has to be hypothesized and must be likely due to impaired leptin transport across the blood–brain barrier [33]. Leptin directly enhances the production of cytokines and interleukins, activates monocytes and macrophages to produce pro-inflammatory agents, and stimulates the production of complement and vascular endothelial growth factor in human hepatic cells [29, 31]. Leptin suppresses insulin secretion in a negative feedback loop where insulin stimulates the release of leptin: by consequence, the development of a leptin resistance with an excess of leptin availability might lead to a decreased insulin action [34, 35]. There can be also a crosstalk between the levels of leptin and adiponectin, and therefore in an uncomplicated obese patient, a negative relationship between serum adiponectin and leptin concentrations has been demonstrated [21, 23].

In the severely obese patients, bariatric surgery raises circulating adiponectin in part simply by decreasing fat mass and by elevating gene expression of adiponectin from the visceral adipose tissue [24, 35–40]. Moreover, in the severely obese patients, after surgically induced weight loss, the serum leptin concentration, after an early marked fall, gradually reduces following the decrease of body weight and body fat size [23, 39, 40] without any evident of direct association with changes in insulin sensitivity [24].

In the subjects of this study, the lack of a negative correlation between BMI by the one hand and serum adiponectin and BMI values by the other observed before surgery supports the hypothesis that, in T2DM, the dysregulation in the cytokine system actually contributes to metabolic derangement [24, 41].

In the T2DM patients undergoing BPD herein described, the serum leptin sharply falls at the first postoperative year and remains essentially unchanged throughout the follow-up

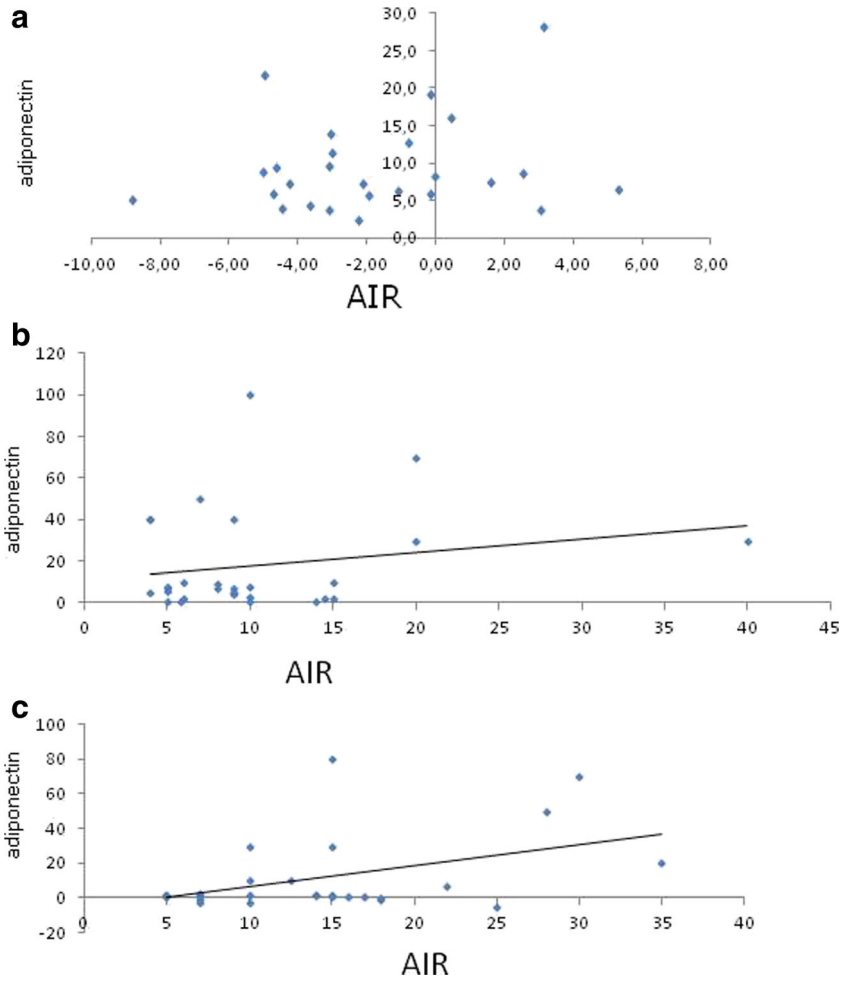

Fig. 2 T2DM patient undergoing biliopancreatic diversion. Association (with trend) between the serum adiponectin concentration and acute insulin response (*AIR*) to intravenous glucose preoperatively (**a**, rho = 1.94, p = ns) and at the first postoperative year (**b**, rho = 0.467, $p < 0.012$) and at the fifth postoperative year (**c**, rho = 0.297, $p < 0.04$)

period: furthermore, the leptin values were positively correlated with the BMI ones before the operation and at any follow-up time. This suggests that, as in the uncomplicated obese subjects, in the T2DM patients undergoing bariatric surgery, the serum leptin level proportionally follows the body weight [23, 39–42]: the serum leptin level results sharply reduced at 1 year after the operation and, at a longer term, being the body weight substantially stable, remain nearly unchanged. Furthermore the serum leptin concentration seems to be completely independent of the metabolic conditions: in fact, the values were strictly associated with body weight at any follow-up point, and in both the patients having reached a positive metabolic outcome and their counterparts with a negative postoperative outcome, substantially similar data were obtained. In the subjects having experienced a long-term T2DM postoperative remission, the serum adiponectin level significantly raised at the first post-BPD year and a further significant increase was observed at a long term, showing a postoperative trend very similar to that found in the uncomplicated obese patients undergoing weight loss surgery [22–24, 35–39]. On the contrary in the T2DM subjects with a negative metabolic outcome, the baseline serum adiponectin values remained unchanged and only a slight and not significant increase was observed at the fifth postoperative year. This suggests that, besides the weight loss and the action of gastrointestinal hormones, a postoperative rearrangement of the cytokine pattern with a reduced chronic inflammation might play a not secondary role in the T2DM remission at a long term after bariatric operation. Previous data have shown that adiponectin enhances insulin sensitivity by increasing the fatty acid oxidation and inhibiting the hepatic neoglucogenesis [18]. However, after surgically induced weight loss, the insulin sensitivity was assessed by a HOMA method normalized in all T2DM patients in spite of different adiponectin concentrations. On the contrary, a positive association between AIR values and serum adiponectin concentration was observed both at 1 and 5 years after the operation, thus supporting the role of adiponectin as an insulin-enhancing factor. Since AIR is not affected by the gastrointestinal physiology, it can be suggested that the postoperative improvement of the cytokine pattern is independent of the enterohormonal action.

Recent studies [40–42] have shown that the increased insulin secretion/production, as evidenced by the AIR values or the disposition index data, plays an essential role in the short-

and long-term remissions of T2DM after BPD. The progressive increase of adiponectin levels in the postoperative T2DM remitter patients and the positive association between insulin action and serum adiponectin concentration after operation suggest a role for the recovery of cytokine balance in the T2DM remission. These longitudinal findings support the previous data obtained in a cross-sectional group of T2DM obese patients: in the subjects with a negative metabolic outcome after bariatric surgery, a lower level of serum adiponectin concentration and a reduced beta cell function were observed in comparison with subjects having reached a complete postoperative T2DM remission [43, 44].

In conclusion, this study suggests that the T2DM remission at a long term after bariatric surgery is accounted for not only by the normalization of insulin sensitivity and by a restored insulin secretion but also by an improvement of the pattern of cytokine production. In fact, an increase of adiponectin serum concentration was observed only in patients who have experienced a positive metabolic outcome at 5 years following BPD, while in the unsuccessful patients, the weight loss was not accompanied by changes in adiponectin serum level. The lack of an evident postoperative increase in serum adiponectin level parallels the failure in recovery of insulin secretion and the negative long-term metabolic outcome. Furthermore, a positive interaction between the improvement of the adipokine pattern and the recovery of insulin secretion secretion/production was observed. Further studies will be necessary to understand whether the trigger cause for the T2DM postoperative recovery after weight loss surgery is represented by the recovery of insulin secretion or by the improvement of the cytokine system pattern.

Compliance with Ethical Standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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