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CLINICAL RESEARCH

# Thyroid Function and Insulin Sensitivity Before and After Bilio-pancreatic Diversion

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**Abstract**
*Background* Bilio-pancreatic diversion (BPD) induces permanent weight loss in previously severe obese patients through a malabsorptive mechanism. The aim of the study was to evaluate the modifications of circulating thyroid hormones after BPD, a surgical procedure which interferes with the entero-hepatic circulation of biliary metabolites.
*Methods* Forty-five patients were studied before and 2 years after BPD. Thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), anti-thyroid antibodies, iodine urinary excretion, lipid profile, insulin and glucose plasma levels were assessed. The insulin-resistance HOMA IR index was calculated, and colour Doppler ultrasonography of the neck was performed.
*Results* The subjects (23%) had subclinical hypothyroidism prior to BPD (TSH levels above the normal range with normal fT3 and fT4 levels). After 2 years 40.42% of the population showed subclinical hypothyroidism, while 6.3% became frankly hypothyroid, all of them with no evidence of auto-immune thyroiditis. Most of the patients, who became sub-clinically hypothyroid only following BPD, had already thyroid alterations at the sonogram (multi-nodular euthyroid goiter and thyroidal cysts) prior to surgery.
*Conclusions* BPD increases the prevalence of subclinical or even frank hypothyroidism, without causing a defect in thyroid function itself, through several integrated mechanisms. (1) It induces iodine malabsorption, which is partially compensated by iodine excretion contraction. (2) The entero-hepatic open circulation determines fT3 loss, which induces subclinical or frank hypothyroidism in patients with pre-existing thyroid alterations, interfering also with the weight loss progress. Iodine supplementation should be recommended in those patients reporting thyroid alterations at the sonogram prior to BPD, LT4 therapy should be strictly monitored in patients suffering of subclinical hypopthiroidism and T3 therapy should eventually be considered for patients diagnosed with frank hypothyroidism prior to BPD.

**Keywords** TSH · Free T3 · Free T4 · Iodine · Bilio-pancreatic diversion (BPD) · Body mass index (BMI)

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## Introduction

Bilio-pancreatic diversion (BPD) is a bariatric procedure which induces permanent weight loss and greatly ameliorates insulin sensitivity in previously severe obese patients, acting through a malabsorptive mechanism [1].

In the recent years there has been an increased interest on thyroid function and changes in body weight. Various studies in literature show a significant positive correlation between thyroid-stimulating hormone (TSH), even within the normal range, and body mass index (BMI) [2, 3]. The major determinant of thyroxine requirement seems to be fat-free mass (FFM), which might induce an increased stimulation of the thyroid in order to maintain normal thyroxine levels. This phenomenon determines a positive

correlation between thyroid volume and FFM, rather than between thyroid volume and body weight itself [3]. Other studies have postulated a positive relationship between TSH and the degree of obesity, suggesting a homeostatic adjustment for excessive adiposity [4], due to the fact that T3 regulates resting energy expenditure (REE), likely by enhancing lipolysis [5, 6]. In the light of this patho-physiological background, subclinical hypothyroidism seems to affect more often morbidly obese people than non-obese subjects [7, 8], contributing, to some extent, to the progression of obesity. In fact, changes of leptin levels as observed in obese subjects determine TRH stimulation, with an increase of TSH levels and a subsequent decrease of energy expenditure [8].

When weight loss occurs, a decrease in the levels of peripheral thyroid hormones is likely to be observed, along with a reduction of REE [9] and changes in energy intake [6, 10, 11]. In fact, variations in peripheral thyroid hormones metabolism have been reported in conditions of energy imbalance, suggesting an impaired peripheral 5′-monodeiodination of T4 to T3 [12].

Studies that focussed on weight loss in patients with acute illness involving protein malnutrition have provided evidence of decreased serum triiodothyronine levels and a reciprocal increase in the serum concentration of reverse triiodothyronine, its inactive metabolite, both derived from thyroxine monodeiodination which occurs mainly in the liver. Since serum triiodothyronine is the active metabolite responsible for energy expenditure, the decreased conversion of thyroxine to triiodothyronine can be interpreted as an attempt to preserve the eu-metabolism [13].

The aim of the present study was to evaluate the modifications of circulating thyroid hormones after bilio-pancreatic diversion, which determines lipid and, even if to a lower extent, protein malabsorption, as well as interruption of the biliary entero-hepatic circulation [14], which represents the main pathway of physiological T3 intestinal reabsorption.

## Research Methods and Procedures

### Subjects

Our study population included 45 severely obese subjects (15 men and 30 women; 43±10 years old, with a mean BMI of 50.58±8.77 kg/m$^2$), studied before and 24 months after having successfully undergone bariatric surgery, in a phase of stabilised body weight (±2 kg variation in body weight in the 4 to 6 months prior to testing), with a mean BMI of 36.24±6.63 kg/m$^2$. None of the subjects had any abnormalities during puberty and physiological development. Diabetes, kidney or liver diseases and other major endocrine diseases (except for subclinical hypothyroidism) were considered exclusion criteria for enrolment. During the present study, none of the subjects were taking any medication, except for L-thyroxine taken by the patients diagnosed with hypothyroidism, either subclinical or frank, and oral vitamin, calcium and iron supplementation prescribed to all patients for the treatment of the chronic malabsorption subsequent to BPD.

Thyroid function (TSH, free triiodothyronine (fT3) and free thyroxine (fT4)), anti-tireoglobulin (Tg) antibodies (Ab) and anti-tireo-peroxidase (TPO) Ab and iodinuria were evaluated before and after BPD, together with insulin resistance (HOMA IR), glucose and insulin plasma levels and lipid profile including total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides and HDL/total cholesterol ratio. Blood samples were collected after an overnight fast. Evidence of TSH levels above the normal range (≥3 μUI/ml) associated with normal fT3 and fT4 levels was diagnostic for subclinical hypothyroidism [15, 16]. This group of patients had higher levels of triglycerides and TSH ($p<0.05$) compared to the rest of the study population, lower levels of FFM, although not significant, and a balanced oxidation of energy substrates (RQ=0.75). Results in terms of weight loss, body composition, lipid profile and substrate oxidation following BPD did not differ between groups. Levels of circulating TSH remained above the normal range, and in some cases increased.

The study protocol was approved by the ethical committee of the Catholic University in Rome, and all participating subjects signed an informed consent.

### Bilio-pancreatic Diversion

This procedure consists of a ~60-cm distal gastric resection with stapled closure of the duodenal stump, as currently described [1], with the proximal end of the ileum anastomosed to the bowel 50 cm proximal to the ileo-cecal valve. Consequently, the total length of absorbing bowel is reduced to 250 cm (so-called alimentary tract).

### Analytical Assays

Plasma glucose was measured by the glucose oxidase method (Beckman, Fullerton, CA, USA). Insulin and c-peptide were assessed by radioimmunoassay using kits from Abbott Diagnostics (Milan, Italy). Serum triglycerides were measured by enzymatic, colorimetric methods. Total, LDL, and HDL cholesterol were measured by automated enzymatic assay. TSH, fT3, fT4, Tg Ab, TPO Ab, and iodinuria assessments were made in the central endocrine laboratory of the Catholic University Hospital as well as total bilirubin, transaminases, albumin and γGT measurements.

The formula used for calculating HOMA-IR was

[Fasting plasma insulin (mIU/l) − fasting plasma glucose(mmol/l)]/22.5

### Colour Doppler Ultrasonography of the Thyroid

Colour Doppler ultrasonography of the neck was performed using an ESAOTE AU5 Harmonic apparatus (Genoa, Italy) equipped with colour and power Doppler and a 10 MHz probe. The sonographic study was carried out with the patient in dorsal decubitus with a cushion under the shoulders and the neck in hyperextension.

### Body Composition

Body weight was measured to the nearest 0.1 kg using a beam scale. Body composition was estimated from total body water (TBW) measurements assayed by isotopic dilution as currently described [17].The isotopic disintegration per minute was counted with a Beta-scintillation counter Canberra-Packard, Model 1600TR (Canberra, CT, USA) in duplicate. To calculate FFM, TBW values were divided by 0.73.

### Respiratory Exchange Measurements

Measurements of the respiratory gas exchanges were performed by continuous indirect calorimetry as currently described [18] (Delatrac, Datex Instrumentarium, Finland). Energy expenditure, non-protein respiratory quotient and substrate oxidation rates were calculated from oxygen consumption, carbon dioxide production and nitrogen urinary excretion [19].

### Statistical Analysis

Data are given as means±standard deviation. Wilcoxon signed ranks test was used to assess significance between pre- and post-BPD values, and one-way ANOVA, with sex as independent variable, was used to evaluate differences between sexes; a two-tailed Pearson bivariate correlation was used to assess simple correlations between parameters. Distribution statistics for the residuals were calculated to check whether assumptions of normality were met (i.e. skewness and kurtosis <2.0). A multiple regression analysis was performed in order to identify independent variables. Variables entered the model if significant at the <0.05 probability level.

## Results

The anthropometric and biochemical characteristics of the study group are shown in Table 1.

No significant differences were observed between sexes, except for HDL cholesterol plasma concentration which, after BPD, decreased in men (from 38.56±10.5 to 34.11± 9.26 mg/dl; $p<0.05$) and increased in women (from 43.03± 11.22 to 46.59±13.21 mg/dl; $p<0.05$). Colour Doppler ultrasonography of the neck showed some alterations in thyroid morphology (10 multi-nodular goiters, three thyroid

**Table 1** Morphometric and biochemical parameters of the population under study before and after BPD (45 patients, 15 men and 30 women)

| | Before BPD | After BPD | Sig. |
|---|---|---|---|
| Age (years) | 41.50±11.02 | 44.23±8.01 | n.s. |
| Weight (kg) | 136.96±24.01 | 98.64±18.89 | $p<0.001$ |
| Height (cm) | 165.04 ±11.31 | 166.20±11.31 | |
| BMI (kg/m$^2$) | 50.28±8.87 | 35.74±6.55 | $p<0.0001$ |
| EE (kcal/24 h) | 2,194.46±479.88 | 1,851.83±365.51 | $p<0.01$ |
| RQ | 0.76±0.02 | 0.79±0.02 | $p<0.01$ |
| FM (kg) | 74.29±18.90 | 45.12±22.03 | $p<0.0001$ |
| FFM (kg) | 62.67±12.27 | 53.52±13.01 | $p<0.01$ |
| FM (%) | 54.25±11.49 | 45.74±17.01 | $p<0.0001$ |
| FFM (%) | 45.75±9.62 | 54.26±10.56 | $p<0.01$ |
| TSH (μIU/ml) | 2.96±4.11 | 4.59±9.05 | $p<0.01$ |
| FT4 (pg/dl) | 12.32±2.59 | 11.85±2.04 | n.s. |
| fT3 (pg/dl) | 3.23±0.49 | 2.78±0.46 | $p<0.0001$ |
| Ioduria (μg/l) | 62.93±16.82 | 42.33±13.20 | $p<0.01$ |
| HOMA IR | 4.56±2.77 | 1.17±0.70 | $p<0.0001$ |
| Glucose (mM) | 5.14±0.73 | 3.93±0.70 | $p<0.0001$ |
| Insulin (μIU/ml) | 19.83±11.61 | 7.72±5.77 | $p<0.0001$ |
| C-peptide (ng/ml) | 4.54±2.24 | 2.05±1.00 | $p<0.01$ |

cysts and five thyroid volume reduction) in 40% of the population studied. According to the currently accepted guidelines for the diagnosis of subclinical hypothyroidism [15, 16], 23.4% of the subjects had subclinical hypothyroidism before BPD with a female to male ratio of 2:1, and none of them had frank hypothyroidism prior to surgery. Subclinical hypothyroid patients received an average levothyroxine supplementation of 125±25 μg.

Two years after BPD, fT4 remained basically unchanged, while fT3 decreased significantly ($p<0.0001$). Twenty-four-hour iodine excretion significantly decreased ($p<0.01$) to values below the normal range (50–150 μg/l). TSH was significantly increased ($p<0.01$), with 40.4% of the patients diagnosed with subclinical hypothyroidism and a female to male ratio of 3:1. Frank hypothyroidism was encountered in 6.3% of the patients, all women. No significant changes were observed at the colour Doppler ultrasonography of the neck after BPD. Levothyroxine supplementation was increased in all the previous subclinical hypothyroid (SH) subjects at an average dosage of 150± 25 μg and was given in average dosage of 112.5±12.5 μg in the newly onset SH subjects. HOMA IR, glucose and insulin plasma levels significantly decreased after BPD, showing a great improvement in insulin sensitivity together with a reduction of insulin secretion. Lipid profile significantly improved, and body composition showed a large reduction particularly of fat mass (FM), as shown in Table 1. No significant differences were observed in terms of weight loss or BPD complications between hypothyroid and euthyroid patients.

With a Pearson simple correlation, TSH levels before BPD were positively correlated with TSH levels after BPD (0.39 correlation value (cv); $p<0.001$) and with insulin sensitivity after BPD (0.41 cv; $p<0.001$). Furthermore fT3 levels before BPD were negatively correlated with FM levels after BPD (0.39 cv; $p<0.05$). In a linear regression analysis weighted by BMI after BPD, in a model including insulin sensitivity after BPD as dependent variable, TSH and fT3 levels before BPD, TSH and fT3 levels after BPD, TSH levels before BPD ($p<0.001$) and fT3 levels after BPD ($p<0.05$) better correlated with insulin sensitivity after BPD ($R^2=0.598$; $p<0.001$).

In another linear regression analysis weighted by BMI after BPD, in a model including FM after BPD as dependent variable and fT3 before BPD, EE, fT3 and fT4 levels after BPD as independent factors, fT3 levels before and after BPD and EE after BPD better correlated with FM after BPD ($R^2=0.844$; $p<0.001$).

## Subclinical and Frank Hypothyroid Population

The biochemical characteristics of the SH population studied are shown in Table 2.

Twenty-three percent of the subjects had subclinical hypothyroidism before BPD. Among these patients, 63.6% were women and 36.4% were men. No difference between sexes was observed, except that only resting energy expenditure differed among sexes, which was higher in men than in women, as expected (2,701±281 kcal/day in men vs. 2,054± 211 kcal/day in women; $p<0.001$). Our subclinical and frank hypothyroid (SFH) population had increased levels of TSH with normal fT3, fT4, total and LDL cholesterol levels, low HDL cholesterol, normal triglycerides and decreased insulin sensitivity prior to BPD. Substrate oxidation showed a marked preference for lipid oxidation (see Table 2).

Two years after BPD, 40.42% of the entire study population had subclinical hypothyroidism (72.7% women and 27.3% men), while 6.3% became frankly hypothyroid (all women), with no evidence of anti-Tg and anti-TPO antibodies. All patients with subclinical hypothyroidism prior to BPD remained SH, and three of them became frankly hypothyroid after surgery despite the oral LT4 supplementation (175–250 μg/day). Since no significant difference in terms of morphometric and biochemical parameters was observed between the subclinical and frank hypothyroid group, they have been considered as a single study population. Most of the patients (63.3%) who became sub-clinically hypothyroid only after BPD had already thyroid alterations at the sonogram (multi-nodular euthyroid goiter and thyroidal cysts) prior to surgery, and none of them had auto-immune chronic thyroiditis either before or after BPD. No differences between sexes were observed. Normalisation of total and LDL cholesterol, triglycerides and insulin sensitivity was achieved after BPD, while HDL remained lower than the normal range. However, HDL/total cholesterol ratio significantly increased after surgery.

Iodine excretion with urine decreased significantly after BPD, with values below the normal range (Table 2), but no significant difference in iodine excretion was found following surgery between patients with or without hypothyroidism. The only predicting factor of fT3 levels after BPD was the low HDL cholesterol concentration ($R^2=0.29$; $p<0.05$). ΔfT3 (Delta, Δ: percentage of decrease below basal values) resulted to be the only factor correlating with weight loss in the SFH population in a model including ΔBMI as dependent factor and post-BPD TSH, ΔfT3 and ΔfT4 as independent variables (linear regression analysis; $R^2=0.47$; $p<0.05$; Fig. 1).

## Population with Normal Thyroid Function (E)

The vast majority of this study population (34 patients) did not have any alteration in thyroid function before BPD. Parameters assessing insulin resistance as well as the lipid profile were similar to those of the SFH population, while plasma levels of triglycerides were significantly lower ($p<0.05$).

**Table 2** Biochemical and metabolic parameters of the two subgroup population (subclinical/frank hypothyroid SFH and euthyroid E) before BPD and after BPD

| | Subclinic/frank hypothyroidism (SFH) | | | Euthyroidism (E) | | |
|---|---|---|---|---|---|---|
| | Before BPD (11 patients) all SH | After BPD (19 patients SH; 3 patients FH) | Sig. | Before BPD (34 patients) | After BPD (23 patients) | Sig |
| Age (years) | 41.18±8.16 | 43.15±8.12 | n.s. | 42±12 | 43.45±9.3 | n.s. |
| BMI (kg/m$^2$) | 48.95±6.67 | 34.65±6.59 | $p<0.0001$ | 50.71±9.53 | 36.88±6.58 | $p<0.0001$ |
| Weight (kg) | 136.51±18.6 | 96.68±18.38 | $p<0.0001$ | 137.19±25.73 | 98.38±17.77 | $p<0.0001$ |
| Height (cm) | 167±10.8 | 167±10.8 | | 164.48±12.01 | 164.48±12.01 | |
| EE (kcal/24 h) | 2,216.38±364.67 | 1,844.22±378.13 | $p<0.05$ | 2,183.50±539.23 | 1,859.44±375.22 | $p<0.01$ |
| RQ | 0.75±0.02 | 0.7986±0.02 | $p<0.05$ | 0.77±0.021 | 0.78±0.02 | n.s. |
| FM (kg) | 75.63±14.46 | 41.34±16.29 | $p<0.01$ | 73.63±21.18 | 47.7±17.92 | $p<0.01$ |
| FFM (kg) | 60.88±7.06 | 55.34±10.02 | $p<0.05$ | 63.56±14.32 | 50.68±11.16 | $p<0.05$ |
| FM (%) | 55.4±11.2 | 42.76±13.1 | $p<0.01$ | 53.67±13.21 | 48.48±11.32 | $p<0.05$ |
| FFM (%) | 44.6±10.1 | 57.24±18.2 | $p<0.05$ | 46.32±12.12 | 51.51±15.3 | $p<0.05$ |
| TSH (μIU/ml) | 5.38±3.57 | 5.21±4.08 | $p<0.05$ | 1.66±0.63 | 1.71±0.7 | n.s. |
| FT3 (pg/ml) | 3.1±0.55 | 2.62±0.47 | $p<0.01$ | 3.26±0.46 | 2.920±0.38 | $p<0.01$ |
| FT4 (pg/dl) | 10.7±2.46 | 11.09±1.25 | n.s. | 12.811±2.46 | 12.54±2.26 | n.s. |
| Ioduria (μg/l) | 63.75±14.36 | 47.6±12.61 | $p<0.05$ | 62.64±18.27 | 41.64±13.9 | $p<0.05$ |
| HOMA IR | 4.60±2.72 | 1.1±0.68 | $p<0.0001$ | 4.55±2.83 | 1.25±0.71 | $p<0.0001$ |
| Glucose (mM) | 5.35±0.94 | 3.82±0.6 | $p<0.0001$ | 5.07±0.66 | 4.01±0.77 | $p<0.0001$ |
| Insulin (μIU/ml) | 19.65±11.3 | 6.45±3.43 | $p<0.0001$ | 19.89±11.87 | 6.47±3.45 | $p<0.0001$ |
| C-peptide (ng/ml) | 5.775±3.74 | 2.25±1.06 | $p<0.05$ | 4.04±1.3 | 1.85±0.84 | $p<0.05$ |

*SH* subclinical hypothyroid, *FH* frank hypothyroid

Two years after BPD, insulin sensitivity significantly increased, lipid profile normalised and fT3 significantly decreased ($p<0.05$), although still remaining within the normal range, while TSH and fT4 underwent no significant modifications without any difference between gender. Urinary iodine was significantly decreased after BPD, with values below the normal range. ΔBMI showed no significant correlation with the changes in thyroid function. Weight loss in the normal thyroid population was similar to that observed in the subclinical and frank hypothyroid population (−29.7±18.34 vs. −29.22±10.48%; $p$=n.s.), but with a higher SD (Table 3). In a linear regression analysis, in a model including ΔBMI as dependent factor and post-BPD TSH, DfT3 and ΔfT4 as independent variables, no variable resulted to be correlated with weight loss, unlike ΔfT3 in the SFH population, in which it seemed to be an independent predictor of weight loss.

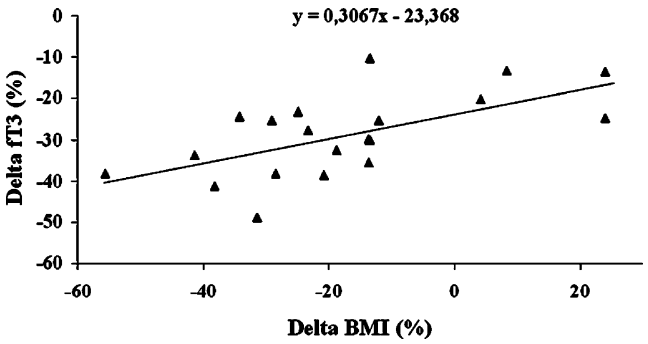


**Fig. 1** Multiple regression analysis in the subclinical/frank hypothyroid population ($R^2$=0.47). The regression line is based on values of patients being diagnosed subclinical or frank hypothyroid after BPD. *Delta BMI* dependent variable, *Delta fT3* independent factor. Delta are expressed as percentage decrease above values before BPD

## Discussion

Our data confirm the observation that morbid obesity is associated with increased TSH (23%) (18), as already reported [7, 8], describing a 25% prevalence of SFH.

Different effects on thyroid function after bariatric surgery have been reported by several authors. Gastric by-pass seems to restore thyroid function in hypothyroid patients independently of final BMI [20–23], while gastric banding seems to reduce TSH levels, with no effect on fT3 and fT4 levels [23, 24]. This phenomenon is often attributed to the loss in body weight, which seems to correlate to TSH levels; however, changes in the nutritional intake interfering with peripheral fT3 de-iodination and modifications of leptin concentrations seem to play a role in

**Table 3** Biochemical and metabolic parameters of the euthyroid population (E) before BPD who remained euthyroid (E) after BPD and those who became subclinical hypothyroid (SH)

| | E pre-BPD who remained E after BPD | | E pre-BPD who became SH after BPD | |
|---|---|---|---|---|
| | Pre-BPD | Post-BPD | Pre-E | Post-SH |
| Age (years) | 42.42±11.12 | 44.45±11.2 | 41.12±11.86 | 43.52±10.95 |
| Weight (kg) | 136.70±29.45 | 98.88±21.51 | 140.60±26.39 | 99.01±20.76 |
| Height (cm) | 169.14±11.54 | | 163.87±14.01 | |
| BMI (kg/m$^2$) | 49.56±9.18 | 35.89±6.76 | 51.59±9.77 | 35.19±9.22 |
| EE (kcal/24 h) | 2,153.12±538.78 | 1,818.63±357.33 | 2,205.25±343.52 | 1,828.57±248.1 |
| RQ | 0.77±0.02 | 0.78±0.01 | 0.76±0.02 | 0.8±0.03 |
| FM (kg) | 74.29±18.16 | 45.08±17.53 | 77.85±21.37 | 51.00±18.55 |
| FFM (kg) | 62.41±12.43 | 53.08±8.34 | 62.75±11.34 | 49.01±5.92 |
| FM (%) | 54.34±8.90 | 45.60±17.30 | 55.37±13.55 | 51.62±10.21 |
| FFM (%) | 45.65±8.82 | 54.40±10.87 | 44.63±8.50 | 48.38±9.30 |
| TSH (μIU/ml) | 1.86±1.11 | 1.80±1.00 | 2.16±0.57 | 4.27±2.97 |
| fT4 (pg/dl) | 12.26±1.92 | 12.42±2.22 | 12.1±2.34 | 11.75±1.17 |
| fT3 (pg/dl) | 3.25±0.36 | 2.85±0.46 | 3.12±10.51 | 2.62±0.46 |
| Ioduria (μg/l) | 62.00±17.56 | 40.58±9.65 | 70.00±17.68 | 51.75±30.40 |
| HOMA IR | 4.66±3.18 | 1.24±0.82 | 3.71±2.00 | 0.86±0.34 |
| Glucose (mM) | 5.34±0.75 | 4.00±0.69 | 5.00±0.57 | 3.78±0.61 |
| Insulin (μIU/ml) | 19.62±13.19 | 7.00±4.30 | 16.92±9.14 | 5.25±2.21 |
| C-peptide (ng/ml) | 4.82±2.28 | 1.92±0.81 | 3.23±1.81 | 1.55±0.55 |

the decrease of TSH secretion. Most frequently a reduction of fT3 levels after BPD is reported, which usually attributed to the significant body weight reduction observed in these patients [13, 23, 24].

One year after BPD an enormous increase of organochlorine pollutants is currently reported in literature [25]. Organochlorines are fat-soluble chemical compounds resistant to degradation that are stored in the adipose tissue of every organism on the planet. When weight loss occurs, lipid mobilisation subsequent to the reduction of fat mass determines an increase in plasma and adipose tissue concentrations of organochlorines leading to various consequences, among which a reduction in triiodothyronine (T3) concentration, resting metabolic rate and skeletal muscle markers for fat oxidation [26, 27]. Although we were not able to measure organochlorine concentration in our patients, the potential effect of these substances on the peripheral conversion of thyroid hormones should be considered as a possible explanation of the worsening effect of BPD on thyroid function in our series.

It is well known that serum thyroid hormone levels drop during starvation and severe illness. While in mild illness only a decrease in serum triiodothyronine levels is observed, severe and lasting illnesses determine a drop in both serum T3 and T4, with no TSH elevation [28] a condition currently referred to as the "euthyroid sick syndrome" or "non-thyroidal illness syndrome". After BPD, almost half of our patients showed a subclinical or frank hypothyroidism, with TSH above range and no or limited decrease of the thyroid secretive function. So far, the progression of hypothyroidism in these subjects could be considered as independent of surgery, and the low circulating levels of fT3 may be a consequence of inadequate LT4 replacement due to altered gut absorption. However, fT3 decrease after BPD could also be interpreted in the light of the surgically induced anatomical modifications of the gastrointestinal tract interfering with the entero-hepatic axis. Free T3 is mainly produced in the liver by T4 de-iodination, excreted with the bile and reabsorbed through the entero-hepatic circulation. The isoform deiodinase 1 found in liver, kidney and thyroid plays a key role in the production of the active hormone T3 from T4 and in the clearance of the metabolite reverse T3 [29]. After BPD entero-hepatic circulation is an open loop, resulting in faecal loss of fT3. This mechanism accounts for fT3 reduction more than the impaired peripheral conversion from fT4, as demonstrated by the strong influence of lipid malabsorption on fT3 levels observed in our series and in current literature [24].

Replacement therapy with LT4 provides only limited benefit in avoiding the progression toward frank hypothyroidism. Due to the large number of newly diagnosed subclinical hypothyroid patients, and in the light of a supposed high fT3 loss through the entero-hepatic open loop, a direct supplementation of T3, coupled with LT4, could be further investigated in clinical trials in patients undergoing BPD due to the great influence of fT3 both before and after BPD, on FM loss.

Insulin sensitivity strongly improves after BPD, independently of weight loss [30]. An explanation of this phenomenon can be provided by the normalisation of early insulin secretion or acute insulin response to glucose, which is currently considered one of the major determinants of beta-cell function, and is linked to some intestinal hormones such as GLP-1, GIP, and adipocyte-derived factors [31, 32]. In our series, a relationship between TSH before BPD and the amelioration of insulin sensitivity after BPD was observed in the entire population, with fT3 levels after BPD playing an important role. It is well known that TSH levels are linked to insulin sensitivity and to insulin secretion in healthy subjects [33]. Furthermore, in obese subjects insulin sensitivity improvement often correlates with an amelioration of thyroid function [34]. We also previously observed that changes in TSH levels after BPD were associated with a resolution of insulin resistance and were mainly due to changes in 24-h leptin levels [35].

Providing this evidence, thyroidal status checking seems to be essential before performing BPD, as it seems to influence the metabolic outcome of the surgical procedure itself and an adequate global thyroidal balance (i.e. TSH, fT4 and fT3 levels perfectly within the normal range) [16] after BPD is also needed to achieve the expected results following bariatric surgery.

Most dietary iodine is reduced to iodide before absorption throughout the gut, mainly in the small intestine, where its absorption is virtually complete and it is not affected in patients with severe bowel malabsorption [36]. Iodinated amino acids, including $T_4$ and $T_3$, are transported intact across the intestinal wall. Short-chain iodo-peptides may also be absorbed without cleavage of the peptide bonds [37]. In both the E and the SFH populations, a significant reduction in iodine excretion was observed. A possible explanation of this phenomenon can be given by the reduced iodine absorption in the small intestine. In order to compensate for the reduced absorption, urinary excretion is significantly decreased to preserve iodine used for the synthesis of thyroid hormones. Our data show that most of the patients with initial thyroid alterations (i.e. multinodular euthyroid goiter and thyroidal cysts in euthyroidism) developed subclinical hypothyroidism after BPD. Furthermore, thyroid secretion is preserved in most of the patients, and only fT3 is significantly reduced in the entire population. Iodine supplementation could be routinely suggested after BPD, together with multi-vitamin complex, in patients having been diagnosed with previous morphological thyroid alterations (even if euthyroid).

We observed a large variability in weight loss after BPD [38], in line with observations from other groups [1, 39]. We attempted to identify predictors of weight loss performing direct assessments of insulin resistance and considering the length of the segment of absorbing intestine excluded by BPD. Our results showed that neither insulin resistance nor the length of excluded intestine were significant predictors of weight loss at 2 years. In the study population, fT3 levels before and after BPD were independent predictors of FM loss after BPD, showing a direct effect of thyroid function before and after surgical intervention on weight loss after BPD, as what commonly occurs in the general population [40]. Only in the SFH group was weight loss after BPD inversely predicted by the decrease of fT3 levels after BPD. Assessment of the thyroid function should be, therefore, routinely investigated when weight loss is not successfully achieved.

In conclusion, BPD is associated with an increased prevalence of subclinical or even frank hypothyroidism through several integrated mechanisms apparently not affecting thyroid function itself. Patients with newly onset hypothyroidism following BDP could merely represent a group of subjects with a natural progression of a pre-existing thyroid disease. On the other side, no difference in iodine excretion was found postoperatively between patients with and without hypothyroidism, and both groups had a comparable decrease in iodinuria. Nevertheless it is important to point out that BPD induces iodine malabsorption, which is partially compensated by a decrease in iodine excretion in order to maintain a normal rate of thyroid hormone secretion. On the other side, the entero-hepatic open circulation determines fT3 loss, which can contribute to the onset of subclinical or frank hypothyroidism in patients with pre-existing thyroid alterations, interfering, to some extent, with weight loss.

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