Mental health, dysfunctional eating pattern and weight trajectory in subjects undergoing bariatric surgery.

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Summary

Studying the mechanisms of weight regain (WR) may provide much-needed insight into sustained obesity management. The aim of this five-year, prospective, multicentre study is to evaluate the association among eating pattern (specifically maladaptive behaviours), certain psychological variables and weight trajectory in the short and long term after bariatric surgery (BS). The study will include 2 groups: 1.- Candidates to primary BS undergoing laparoscopic gastric bypass (LGBP) or laparoscopic sleeve gastrectomy (LSG) from September 2020 to September 2022. This group will be evaluated prior to surgery, at 4 months, 1 year, 3 years and 5 years after BS and 2.- A control group of subjects with obesity not candidates to BS matched with the intervention group for age, sex and BMI prior to BS. The primary variable will be: Body weight: total weight lost (%), excess weight lost (%), total weight regained (%), excess of weight regain (%). Information regarding the psychological and behavioural variables will be collected using questionnaires that have been validated in our setting and will be completed by the patients themselves online.

Introduction and update on the subject

Obesity is one of the main health problems today, with a prevalence of 20-30% in many European countries. Obesity is a chronic, progressive disease without cure that requires specific treatment for weight loss and continuous follow-up to avoid weight regain [1].

The objective of the treatment of obesity is to achieve significant sustained weight loss (WL), without undernourishment, and with an improvement in body composition and associated comorbidities. In this context, bariatric surgery (BS) is, at present, the only effective treatment to achieve marked and sustained WL in patients with severe obesity, typically yielding a long-term sustained weight losses of 25 to 35% of initial weight [2].

Although the mean data support the effectiveness of BS in the treatment of obesity, the magnitude of WL and the maintenance of weight reduction after BS notably differ among individuals, even among those undergoing the same surgical technique [3]. Data from the pivotal Swedish Obese Subjects (SOS) study show that the maximum WL after BS ranged between -95.5 and + 2.0 kg, and weight regain (WR) after nadir was between 0.0 and 51.4 kg[4]. This heterogeneity in weight trajectory leads some patients to present lower WL than expected and/or the recovery of an important amount of weight after nadir.

At present, it is recognised that the magnitude and maintenance of WL are important to the health results of BS. However, one the main problems encountered is how to define insufficient WL and pathological WR after BS. A systematic review described that the most frequent definition used for insufficient WL after primary BS is a WL < 50% of the excess weight present prior to surgery with or without a body mass index (BMI) > 35 kg/m^2 at 18 months after surgery [5]. Thus, insufficient WL is not just the absolute WL but rather the deviation of WL from the result that is usually achieved after BS.

Likewise, in relation to the definition of WR, several studies have used different definitions based on kilograms, units of BMI**,** or percentage of excess WL regained after nadir or at different time points, including: regain of 10 kg, regain of 25% of excess WL; regain of 15% of initial WL; regain of 5 kg/m2; any WR with a BMI >35 kg/m2 at nadir, at 18 months or 3-5 years post-BS [6]. Patients who show WR present a relapse of not only obesity but potentially also the co-morbidities which had remitted during the initial WL. In this case many require revisional surgery or a second procedure to re-achieve WL, either with RYGB, or another procedure such as duodenal switch at the expense of adding a malabsorptive component to the surgical process, which risks extra complications and a high rate of nutritional deficiencies (Annex 1).

The variability of WL or WR has been associated with a wide range of factors related to the surgical technique used, psychological factors, behavioural, dietetic factors, physical activity and comorbidities as well as biological factors which regulate food intake, energy storage and expenditure [7]. Variables such as previous weight, age and the type of surgery explain between 40-50% of the variance in WL, with the rest

remaining from the variance due to other variables. Although the influence of behavioural and psychological factors are of note in studies on WL after BS, the identification of predictors is not conclusive or has shown a weak relationship.

Despite recognition of the important influence of psychological factors on the results of BS at a weight level, there are no conclusive data to date [8]. The inconsistencies of the results seem to be due to different methodological factors such as the definition of the alterations, the evaluation methods used – clinical interview, psychometric tests, among others – the different time of evaluation, the time reference assessed and the willingness of the candidates to respond in the context of the request for BS. Recent systematic reviews have suggested a certain predictive capacity of some factors on weight results in regard to their influence on eating behaviour after BS (i.e. presurgical cognitive functioning, personality, mental health, some psychological variables and dysfunctional eating behaviours) [9][10]. Therefore, not all patients report benefits in the psychological domain. In some cases, previous pathology may recur or a new psychopathology may arise, impairing the quality of life and interfering in achieving the goals proposed. It is not known whether there is a characteristic profile in patients with insufficient WL or WR after BS.

Thus, within the context of the increasing use of BS it is essential to determine the causes for this variability in weight trajectory following BS and understand what factors have an impact on WR after BS in order to minimise and prevent them. As mentioned previously, behavioural and psychological factors are especially important and require the most attention in order to understand the influence these factors have on WR.

Objective:

The **objective** of this study is to evaluate the association among eating pattern (specifically maladaptive behaviours), certain psychological variables and weight trajectory in the short and long term after bariatric surgery.

Design

Five-year, prospective, multicentre study.

The study will include 2 groups:

a) Candidates to primary BS undergoing laparoscopic gastric bypass (LGBP) or laparoscopic sleeve gastrectomy (LSG) from September 2020 to September 2022. This group will be evaluated prior to surgery (a period vulnerable to biases by the request for surgery that affect the answers to the questionnaires for fear of being contraindicated for surgery). The subjects of this group will be followed at 4 months, 1 year, 3 years and 5 years after BS.
b) A control group of subjects with obesity not candidates to BS matched with the intervention group for age, sex and BMI prior to BS.

*The control group will be recruited by each investigator (10 subjects) and will be evaluated once. According to our casuistic, in order to be comparable with the

intervention group 80% should be women of 45 years of age with a BMI > 40 kg/m^2. This group is needed to adjust for variables such as motivation, patient expectations related to surgery and the effect of surgery.

Inclusion criteria:

- Candidate to primary BS from 09/2010 to 09/2021.
- Subjects with obesity ($\geq$40 kg/m^2) not candidates to BS.
- Internet users.
- Primary BS: LGBP and LSG.
- Accept to participate in the study and provide signed informed consent.

Exclusion criteria:

- Second time and/or revisional BS.
- Pregnancy.
- Presence of intellectual impairment impeding the administration of the psychometric tools.
- Type 1 diabetes.
- Dyslexia.

Weight variables: definitions.

a) The different weight variables will be calculated as follows:

- Weight lost (kg): Pre-BS weight – weight at nadir.
- Current weight lost: Pre-BS weight - current weight.
- Ideal weight: weight corresponding to a BMI = 25 kg/m^2.
- Excess weight lost (%): (Pre-BS weight - current weight)/excess weight [(pre-BS weight – ideal weight) x 100].
- Total weight lost (%): (pre-Bs weight – current weight/pre-BS weight) x 100.

b) To study WR the following variables will be calculated:

- Total WR (%): (100/(pre-Bs weight – weight at nadir)) * weight regained (kg).
- Excess WR (EWR %): [(current weight – weight at nadir)/excess weight] x 100
- Weight regained (Kg): current weight – weight at nadir.

Excess weight lost > 50%, total weight lost > 25% and Excess weight regain > 15% will be considered as significant.

Psychological evaluation:

Information regarding the psychological and behavioural variables will be collected using questionnaires that have been validated in our setting and will be completed by the patients themselves **online** at:

https://www.surveygizmo.eu/s3/90152075/Patient-Survey.

The questionnaires include a total of 201 questions, and the survey is designed to be completed within 30 minutes. On average, 40 questions of this type can be answered in 10 minutes.

To assess hedonic response to the foods, the following questionnaires will be used:

- The subscale of external signal-triggered eating of the Dutch Eating Behaviour Questionnaire (DEBQ) that includes 10 questions.
- A food addiction questionnaire (Yale Food Addiction Scale II) with 25 questions.
- The Bulimia Investigatory Test Edinburgh (BITE) made up of 2 subscales of symptoms and severity including 33 questions.
- There will also be questions related to snacking/nibbling.

The following will be used to assess mood state, stress and negative emotions:

- Dutch Eating Behaviour Questionnaire (DEBQ) which evaluates eating styles and takes into account 3 subscales: external, restrained (10), and emotional eating (13) including a total of 23 questions.
- Positive and Negative Affect Schedule (PANAS) to assess the positive and negative effects of emotional experience including 20 questions.
- Barrat impulsivity Scale (BIS-11) which evaluates impulsive tendencies in 3 dimensions: cognitive, motor and lack of planning and includes 30 questions.
- The consumption of toxic substances will be determined using the following questionnaires: Alcohol Use Disorders Identification Test (AUDIT-4) including 4 questions in which data on the frequency and quantity of alcohol consumed will be obtained, and the Fagerström Nicotine Dependence Scale including 6 questions.
- The Eysenck Personality Questionnaire - Revised (EPQ-R) with only the dimension of neuroticism including 23 questions.

These variables will be considered as confounding psychological variables and will, therefore, be controlled by statistical tests.

- Depression: evaluated with the Hospital Anxiety and Depression Scale (HADS) including 14 questions.
- Perceived economic status, assessed using a visual analogue scale of 10 cms with markings at 0, 5, 10 cm without numbers.

- The International Physical Activity Questionnaire (IPAQ) including 7 questions to assess physical activity.
- Social support evaluated by the evaluation protocol using the English Longitudinal Study of Ageing study. APGAR (including 5 questions).
- Quality of life evaluated using the Impact of Weight on the Quality of Life - Lite (IWQOL-lite) questionnaire including 31 questions.

Table 1: Questionnaires on hedonic response to food, addictive behaviour and mood state.

Hedonic response to food	**Mood state, stress, negative emotions**
DEBQ-external (10)	DEBQ-restraint and emotional (23)
Yale Food Addiction Scale II (25)	Positive and Negative Affect Schedule (PANAS) (20)
Binge eating scale (BITE) (33)	Barrat Impulsivity Scale (30)
Confounding variables	Alcohol Use Disorders Identification Test (AUDIT-4). Fagerström Nicotine Dependence Scale (6)
International Physical Activity Questionnaire (IPAQ) (7).	EPQR-neuroticism (23)
APGAR (5)	Hospital Anxiety and Depression Scale (14)
Quality of life evaluated with the Impact on Weight on the Quality of Life – lite questionnaire (IWQOL-lite) (31)	

Evaluation of food intake: The patients will also complete a registry of foods and drinks consumed over 3 days including a weekend day. It should include the type of food, cooking method, and portion size or weight. Afterwards, the total intake and by macronutrients will be analysed with the Diet Source software (Nestle Health Science. V4.0).

Primary variable:

Body weight: total weight lost (%), excess weight lost (%), total weight regained (%), excess of weight regain (%).

Data collection:

I. Additional information on demographic and anthropometric characteristics and on comorbidities both prior to BS and their evolution over time will be collected in an Excel datasheet designed with this objective and will include the following:

Centre: A number identifying each centre has been assigned starting at 1, with the first 9 numbers having a 0 before them.

Code: To register the data of the patients a 5 digit code will identify each patient, with the first 2 numbers corresponding to the number assigned to the centre and the following 3 numbers will correspond to the number assigned to the patient upon entry in the study. For example, the first patient recruited in Hospital Clinic (corresponding to 04) will be assigned the code 001 so that the final code of this patient will be 04001. The code will be kept in each centre and confidentiality will be guaranteed by the investigator.

The Excel database will not include the number of the clinical history of the patient or any data which could identify the patient.

Study group: 0: control; 1: case

The investigator in each centre should register whether the number of the patient corresponds to a case or a control.

Age: in years

Sex: 0: man; 1 woman

Ethnicity: 0: Caucasian, 1: Gypsy; 2: Latin American; 3: other.

Marital status: 1. Married or with partner; 2. Single; 3. Separated/divorced; 4. Widow.

Lives with (number of people): 1. Alone; 2. Partner/husband/wife; 3. Children, number …; 4. Parents; 5. Elderly parents/in-laws; 6. other

Occupation: 1. Homemaker; 2. Unskilled worker 3. Skilled worker. 4. Administrative, 5. Contract worker; 6. Retailer; 7. Business person; 8. Other.

Current occupational status: 1. Active/remunerated work; 2. Unemployed; 3. Retired; 4.Temporary work leave; 5. Permanent work leave; 6. Disability.

Level of education: The highest level of education achieved will be registered. 1. No education; 2.- primary; 3. secondary; 4. technical training or similar; 5. university; 6. other.

Comorbidities registered prior to surgery:

- Diabetes:

0: normal;

1: altered fasting glucose /intolerance to carbohydrates or previous gestational diabetes;

2: Type 2 diabetes;

3: Type 2 diabetes with HbA1c > 8% 4: insulin treatment.

If a patient classifies as more than one category, this should be separated with a comma. For example, the patient has type 2 diabetes treated with insulin + HbA1c > 8, this would be 2,3,4.

- Sleep apnoea

0: normal or Epworth score < 10;

1: Epworth > 10, apnoea-hypopnoea index 5-20;

2: Use of continuous positive airway pressure therapy (CPAP);

3: Cor pulmonale.

- Arterial hypertension (AHT):

0 Normotensive (blood pressure (BP) ≤ 140/90 mmHg);

1: treatment with 1 hypotensive drug;

2: treatment with more than 2 drugs;

3: decompensated AHT > 140/90 mmHg.

- Dyslipidaemia:

0: no;

1: treatment with statins;

2: treatment with fibrates;

3: treatment with statins + fibrates.

- Hight-density lipoprotein (HDL) level ≤ 40 mg/dl: 0: no, 1: yes.
- Previous cardiovascular events: 0:no; 1: yes .

Psychiatric disorder: 0: no; 1: yes. Add diagnosis.

Variables of weight: Weight in Kg and height in metres at baseline in the two groups; weight at 4, 12, 36 and 60 months in the intervention group and in the control group.

These data will be used to calculate the absolute WL, % of WL, EWL, BMI lost, the total weight regained (TWR) and the EWR .

Surgery: 0: GBP, 1: LSG

Date of surgery: This will be registered as a date and is in order to adapt the dates of the follow-up visits to the different times.

Follow-up: at 4-6 months, and 1, 3 and 5 years

Diabetes yes/no; diabetes treatment (0: no; 1: metformin, 2: DPPIV inhibition, 3: iSGLT2, 4: Sulfonylureas , 5: GLP-1 analogues, 6: insulin). Likewise, combined treatment

should be separated with a comma. For example, a patient controlled with metformin + iSGLT2 would be 1,3.

AHT yes/no; AHT treatment (0: no; 1: treatment with 1 drug; 2: treatment with > 2 drugs);

Dyslipidaemia: 0: No, 1: Yes; treatment: 0: no, 1. Treatment with statins, 2: treatment with fibrates, 3: treatment with statins + ezetimibe.

Sleep apnoea hypopnoea syndrome (SAHS) yes/no; Use of CPAP yes/no;

Revision surgery: 0: no, 1: yes.

Date of revision surgery: registered in date format.

Analytical parameters: fasting glucose, insulin, HbA1c, creatinine, total cholesterol, HDL.

Bioimpedance: fat mass (FM) %; FM kg; fat free mass: (whatever is available).

Sample size

The study will include 445 patients undergoing BS. It is estimated that the percentage of losses to follow-up at 5 years will not be greater than 10% and thus, at least 400 patients must achieve complete follow-up. This sample size will have a statistical power of 80% for detecting an effect size, that is, differences divided by the standard deviation of at least $\geq$ 0.281[11]–[13] in magnitude; this effect size is considered in the literature as being of small magnitude [14], [15], and consequently the statistical power will be greater for greater magnitudes. The study will also be discriminatory for binary variables presenting an association with an odds ratio (OR) of at least $\geq$ 1.78[11], [16], [17]. Finally, correlations $\geq$ 0.6[18]–[21] will be detected considering that values < 0.5 are not relevant. In the three cases cited the calculations of sample size were made using a bilateral level of significance of 5% and a statistical power of 80%. This sample size will allow adjusting possible confounding factors and generate a multivariate model with a minimum number of covariables (at least 4-7, depending on the final number of events and correlations) to obtain adjusted estimators [22]–[24].

Additionally, 100 controls not undergoing BS will be included and matched for age, gender and BMI with the objective of standardising the values in the scales. The ratio will be 1:4 for controls and patients undergoing BS, respectively.

Statistical analysis

The design and statistical analysis of the present study meet the recommendations of consensus documents in the literature [25]–[28], specially the TRIPOD statement [29]. A statistical analysis plan (SAP) will be elaborated [30] prior to finalisation of data collection and will provide an in depth description of the statistical methods to be used, the tables and figures that will be included in the statistical report as well as the

strategy to follow in the case of missing values [31], [32], and multiplicity [33] adapted to regulatory [34] and scientific recommendations [26].

Descriptive statistics will be used according to standard calculation methods [35]. To elaborate a predictive model to a determined time, logistic regression models will be used [36]–[39]. For time variables up to a determined event, survival analysis techniques will be used. The function of survival as well as the median of time to the event (confidence interval of 95% [CI 95%]) will be estimated using the Kaplan-Meier method. Estimations of risk will be made with the classical [40] and extended [41] Cox proportional hazards model. Covariables will be tested for the assumption of proportional hazards. Initially all the possible covariables will be analysed in a univariate analysis, and factors with $p < 0.1$ will be included in a multivariate model. All the variables not selected for inclusion ($p >= 0.1$) will, in turn, be checked in the final model to determine whether their inclusion would improve adjustment of the model by a p value < 0.1 or a value less than Akaike. Continuous variables will be tested as continuous linear variables, categorical variables (that is, quartile and predefined for clinical reasons) or continuous non-linear variables based on previously published literature, clinical value and goodness-of-fit models.

The following is a summary of the general approach of inferential statistical analysis. The Fisher exact test will be used to compare categorical variables. For continuous variables between the two groups, the Student's t test and ANOVA for more than two will be used. In the case of not fulfilling the assumptions of applicability or of ordinal variables, non-parametric methods (Mann-Whitney U test or Kruskall-Wallis) or an ANOVA will be used with previous transformation of the dependent variable to ranges to evaluate more than one factor concomitantly (rank-ANOVA).

Variables repeated over time will be analysed as follows: (i) continuous variables, such as the evolution of the variables of weight, with longitudinal mixed model for repeated measurements (MMRM)[42], [43]; (ii) Binary variables will be analysed using Generalised Linear Mixed Models (GLMM). Marginal models will be used (Generalised Estimating Equation (GEE) for the analysis of sensitivity [44][45].

The results will be analysed with the SAS version 9.4 statistical package (or a higher version) [46] (SAS Institute Inc., Cary, NC) or with equivalent validated software. The level of significance will be bilateral at 5%.

Ethical Committee

The protocol should be approved by the Ethical Committees of the participating centres. An informed consent sheet will be included together with the project for presentation to the Ethical Committee of each centre. Informed consent will include special emphasis on the confidentiality of the personal data and that these data will not be able to be identified. Following receipt of approval, the investigators must send a copy of the approval and the number assigned for incorporation in the project file. The original should remain in the centre and its safety is the responsibility of the centre investigator.

The results of the centres that do not obtain approval from the Ethical Committee will not be used in the analyses.

Treatment of missing data

Missing data will be registered in box x to ensure that the data cannot be recovered. If the box remains empty, there will continue to be doubt about whether the data can be recovered.

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