DOES BARIATRIC SURGERY IMPROVE CARDIAC AUTONOMIC MODULATION ASSESSED BY HEART RATE VARIABILITY? A SYSTEMATIC REVIEW

BARIATRIC SURGERY AND HEART RATE VARIABILITY

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ABSTRACT

OBJECTIVES: Our study aimed to explore the influence of Bariatric Surgery (BS) on heart rate (HR) variability (HRV) through a systematic review. **DATA SOURCES:** Manuscripts were selected based on electronic searches of MEDLINE, EMBASE and CINAHL databases from the inception of each database up to year 2020 and followed the PRISMA protocol. Searching of these studies was systematized using the PICOS strategy. **ELIGIBILITY CRITERIA FOR SELECTING STUDIES:** We selected randomized and non-randomized controlled trials and cohorts' prospective studies that reported the influence of BS on HRV. We assessed the quality rating using the Black and Downs questionnaire. **RESULTS:** Following the screening and eligibility stages, 14 studies were included in the review. All studies agreed that BS promotes an increase in parasympathetic HR control and HRV and, a decrease in HR. Yet, the literature does not provide evidence that this outcome was directly caused by the surgical procedure. There is limited evidence to support that patients with type 2 Diabetes Mellitus (TDM2) have greater improvement in HRV as an interim measure, to individuals without. The decrease in insulin resistance was correlated with the increase in HRV in some studies, but, other studies are unsupportive of this outcome. Improvements in two metabolic parameters (e.g., Leptin, NT-proBNP) were connected with a superior increase in HRV. **SUMMARY/CONCLUSION:** This review demonstrated that BS promotes an increase in HRV, indicating improved autonomic control of HR.

Key-words: Bariatric Surgery; Obesity; Heart Rate Variability; Rehabilitation; Cardiovascular Physiology; Metabolic Diseases.

INTRODUCTION

Cardiovascular activity is partly regulated by afferent and efferent nerves in the subdivisions (sympathetic and parasympathetic) of the autonomic nervous system (ANS) [1-7]. The ANS has the important role of modulating cardiac activity and adapting it on different occasions, through excitatory and inhibitory stimuli [5,8]. These reflexes under normal conditions are modulated with a high degree of precision and speed [3,8-9].

HRV is a non-invasive technique to assess cardiac autonomic function via the quantification of the oscillations in milliseconds between consecutive RR-intervals of sinus origin. These values are applied in mathematical formulas that generate HRV indices. [10-12]. HRV is considered one of the most reliable and robust techniques for assessing the autonomic balance [9,13-14]. Changes in HRV are applied as a sensitive and early indicator of impairment in physiological homeostasis [15]. High HRV is a sign of good ANS adaptation and characterizes a healthy individual, with efficient autonomic regulation. Conversely, low HRV is frequently a sign of incapacity and insufficient adaptation of the ANS, manifesting a physiological malfunction [12].

Part of the cardiovascular burden promoted by excess body mass involve changes in autonomic nervous system (ANS) control [16-17]. In obese individuals, HRV is reduced, which is produced by a reduction of vagal (parasympathetic) flow and an increase in sympathetic drive [16,18-19]. A reduced HRV is associated with alterations in cardiac function (e.g., increases in HR and blood pressure) and structure (e.g., left ventricular hypertrophy, left atrial enlargement), increasing the risk of cardiovascular diseases and events (e.g., heart failure, arrhythmias, stroke, and myocardial infarction) [16,17,18].

The cardiovascular disturbance triggered by autonomic dysfunction in obesity highlights the importance of therapeutics targeting autonomic function during obesity management [20,21]. Bariatric Surgery (BS) is the gold standard treatment for weight loss in persons with severe obesity (BMI ≥35kg/m²) [22] in a short period and, with a long-term durability [23-27]. The American Society for Metabolic and Bariatric Surgery (ASMBS) reported an annual and upward growth of BS [28] procedures, as other approaches (e.g., drugs, restrictive diets), have been unsuccessful in reducing weight [29,30], and maintaining this loss over an extensive period of time [31,32].

The research by Karason *et al.* [33] was ground-breaking in evaluating the metabolic effects produced by BS in the restoration of HRV. Since then, other studies have determined to investigate the effects of different types of BS (e.g. Roux-en-Y, Vertical Sleeve, Biliopancreatic Diversion, Duodenal Switch and Adjustable Gastric Band) on restoring autonomic control of HR [34-47]. In a corresponding way, recent experiments have correlated the improvement of HRV with other physiological variables that have implications for the morbidity profile of obesity (e.g., Leptin, GLP-1, NT-Pro-BNP, Insulin Resistance) as they have an affinity with the cardiovascular functioning [34,36-42].

Nevertheless, thus far, no study has anticipated investigating the techniques needed to access HRV after BS in primary studies and, what are the effects of different types of BS techniques on HRV? It is unclear if there are major changes in HRV after BS in populations with specific characteristics (e.g., type 2 Diabetes Mellitus (TDM2) and insulin resistance (IR)). Additionally, no article explores and accumulates information regarding the modification of metabolic parameters that were correlated with the improvement of HRV.

So, we performed the first systematic review to assess the effects of BS on HRV with the aim of investigating:

1. the HRV analysis methods performed in primary studies;
2. the effects of different types of BS on HRV; and,

3. the implication of metabolic conditions (e.g., IR and TDM2) and metabolic parameters (GLP-1, Leptin, NT-proBNP) that were previously related to HRV.

METHODS

This review was conducted via a systematized search, from June 2020 to December 2020. The following databases were accessed: EMBASE, MEDLINE (via PubMed) and CINAHL. The review was performed according to the protocol Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) [48]. The protocol for this review was published on International Prospective Register of Systematic Reviews (PROSPERO) under Protocol registration number CRD42020194156.

Search strategy

The search of the articles was performed via the keywords obtained by the Medical Subject Headings (MeSH) and others search terms. The search and selection of the studies were completed using the Population (P) Intervention (I) Comparison (C) Outcome (O) Study Design (S) (PICOS) strategy. The search strategy was defined with MeSH and search terms allocated in each category according to its search characteristic: P – Obesity, I – Bariatric Surgery, C – Non-surgical procedure, O - Heart rate variability, S – Interventional Studies (Randomized trials, non-randomized controlled trials) and Observational studies (cohorts, prospective and longitudinal studies).

The following search terms were applied: “Obesity” AND “Bariatric Surgery” OR “Gastric Bypass” OR “Gastric Banding” OR “Gastric Sleeve” OR “Duodenal Switch” AND “Heart Rate Variability” OR “Autonomic Nervous System” OR “Autonomic Dysfunction” OR “Sympathetic Nervous System” OR “Parasympathetic Nervous System” OR “Vagal Nerve” in their titles and/or in their abstracts.

Screening and Study Eligibility Criteria

The returned studies were screened by applying search criteria in the databases, via the following filters: studies undertaken from the inception of each database until year

2020 and research performed on human subjects. In sequence, the studies identified in the databases were screened by reading their title and abstract.

The final selection phase for inclusion of the articles was undertaken by reading the articles in full (eligibility), performed by two independent researchers (CJRB and YMMP). If there was discrepancy about the inclusion of a particular article, an extra reviewer (VEV) was consulted for a final choice. The eligibility criteria for the studies are determined below:

Patients (subjects)

Adults, male and female (between 18 and 70 years of age) with body mass index (BMI) ≥30kg / m² and that undertook a BS intervention were selected for inclusion.

Intervention

We considered several types of bariatric surgery: “Roux-en-Y gastric by-pass (RGB)”, “Vertical Sleeve Gastrectomy (VSG)”, “Biliopancreatic Diversion (BPD)”, “BPD with a Duodenal Switch (BPD- DS)” and “Adjustable Gastric Band (AGB)”. Surgical procedures could include a form of open surgery (laparotomy) and the minimally invasive (laparoscopic) procedures.

Control

When applicable the control group was defined as any group that was unable to perform BS. In the Braga et al. [34] study, the control group received pharmacological treatment. Whereas, in the studies by Lips et al. [40], Bobbioni-Harsch et al. [42] and Nault et al. [45] the participants control was only followed for the same period, but no treatment was applied. For the other studies, individuals were their own controls before and after BS.

Study Design

Interventional studies (randomized and non-randomized controlled trials), and observational studies (prospective cohort studies).

Data Analysis

The main consequence was the deviations produced in the HRV and HR (beats per minute) by the surgical procedure.

For the analysis of cardiac autonomic control, we measured linear indices (time and frequency domain) and the nonlinear indices of HRV [49].

Time domain: RMSSD = square root of the mean of the square of the differences between adjacent normal RR intervals; SDNN = standard deviation of all normal RR intervals recorded in a time interval, expressed in ms; SDANN = the standard deviation of averaged RR intervals over a 5-minute period; pNN50 = percentage of adjacent RR intervals with a difference in duration greater than 50ms); NN50 = number of NN intervals differing by more than 50 ms. Frequency domain: HF = high frequency component of power spectral analysis with variation from 0.15 Hz to 0.44 Hz in absolute units (ms^2) and normalized units (n.u.) (vagal component); LF = low frequency component with variation between 0.04 and 0.15 Hz in absolute units (ms^2) and normalized units (n.u.) (sympathetic drive); LF/HF = relationship between low and high frequency components (sympathetic/vagal balance). Linear (geometric indexes): HRVi = triangular index calculated from the total number of all NN intervals divided by the height of the histogram of all NN intervals. TINN = Triangular Interpolation of NN intervals histogram. Poincaré-plot indexes: SD1 = standard deviation of the instantaneous variability of the beat-to-beat heart rate; SD2 = standard deviation of long-term continuous RR interval variability; SD1/SD2 = The ratio of SD1 over SD2 (balance of parasympathetic nervous system (PNS) to sympathetic nervous system (SNS) - PNS/SNS tone); Nonlinear (complexity indexes): SampEn =

Sample Entropy [50,51]; DFA = Detrended fluctuation (fractal) analysis of RR intervals [52,53].

The documents that completed the entire analytical process and were suitable for this review had their data extracted in a table with a description of the characteristics of the study population, intervention and outcomes (Table 1).

Quality Rating

The Downs and Black [54] questionnaire was performed to assess the value of the studies. The evaluators independently judged the quality of the studies using the checklist and then any discrepancies in the classifications were discussed to arrive at a final score for each study. This tool is divided into five domains: "report of articles", "external validity", "bias", "confounding variables" and "statistical power" (Table 2). We selected this tool as it can be applied to interventional and observational studies [54]. Two different members of the research team (CJRB and YMMP) studied each article in duplicate.

RESULTS

Study Selection

A total of 392 studies were identified through the searches in all the five databases. Following removal of duplicates (*n*=85), 307 publications were screened for inclusion. Of these, 279 records were excluded after reviewing their title and/or abstract. The remaining 28 papers were selected for full text reading and seven were excluded because the characteristics of intervention were unclear; five articles used inadequate measurement methods and two were excluded because of an unspecific procedure of BS. Finally, 14 studies were included in the systematic review. The search process and selection steps are illustrated in the Flow Diagram of the PRISMA protocol (Figure 1).

Figure 1. Flow diagram of the Prisma protocol with search process and selection steps.

Description of the features of the study population, intervention and outcomes is illustrated in Table 1.

Quality Assessment

The evaluation of the Downs and Black Checklist for Quality Assessment is stated in Table 2.

The percentage agreement between the two researchers who assessed the quality of the 14 studies was 92.85%. The quality ratings of the included studies are revealed in Table 2. The ratings ranged from 17 to 23 (out of a possible 27). Throughout the analysis was included ten prospective cohort studies and two non-randomized controlled trials. No study has attempted to blind patients to the intervention received or blind evaluators who assessed primary outcomes and, so, the results should be considered with these methodological limitations in mind.

Assessment of HRV

HRV measurements were performed within 7 days and 12 months after the BS procedure. Right now, the studies demonstrated heterogeneity throughout the periods when HRV was measured after performing the BS procedure. So, there is no way to assess when changes in HRV occur most prevalently after the BS procedure, considering the discrepancies between the intervals at which HRV was computed.

Only one study measured HRV before (7 days) metabolic changes occurred and, thus, there is no evidence to support that the effects produced by HRV are directly induced by the surgical procedure.

HRV was assessed in a comprehensive manner using five studies through Holter ECG, [37,41,43,44,45] followed by the Electrocardiogram (four studies) [35,38,39,40]. One study applied Plethysmography [34], another study enforced the Polar RS800CX HR monitor [46]. Only one study used the VariaCardio T4 device [47], another study assessed HRV by Echocardiography [42]. Lastly, one study did not report the apparatus used to collect HRV whatsoever [36].

Seven studies were performed during the rest period considering a recording between 5 to 30 minutes of HRV duration [34,35,38,39,40,43,46]. A further five studies [37,41,42,44,45] performed the recording of HRV for 24 hours, and two studies did not report the recording time [36,47]. Altogether, 9 studies cited the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) as a reference for studying HRV, but, only one study described the filtering methods employed in the recorded RR time-series.

One or more parameters in the time domain were applied in twelve studies and parameters in the frequency domain in six studies. In five studies, HRV parameters were enforced in the domain of time and frequency. Only two studies applied non-linear HRV parameters.

The most frequently enforced HRV parameters in the time domain were RMSSD (eleven studies) and SDNN (eleven studies). The frequency domain parameters most frequently applied were HF potency in absolute or normalized units (six studies), LF potency in absolute or normalized units (six studies) and the LF/HF ratio (six studies). The most widely used non-linear index was Sample Entropy (two studies). Poincaré-plot indices (SD1, SD2 and SD1/SD2) were enforced in three studies. The deviations in the follow-up period after BS are illustrated in Table 3. HR (bpm) was recorded in ten studies. All of these verified that there was a reduction in HR after the completion of the BS.

Bariatric Procedures

Generally, all combined BS (e.g., RGB and AGB, and RGB and SVG) or isolated (e.g., RYGB, SVG, BPD-DS) surgical methods employed in the experiments were effective in improving HRV following weight loss (Table 3).

Diabetes Mellitus and Insulin Resistance

Despite limited evidence, studies by Lips *et al.* [40] and Casellini *et al*. [36] identified that the increase in HRV arises earlier in patients with TDM2 when compared to patients without TDM2 in the same cohort, occurring at 3 weeks and 12 weeks, respectively.

Amongst the selected studies, five performed correlations between decreased insulin resistance and glucose levels with increases in HRV. Studies by Maser *et al.* [39], Perugini *et al.* [41] and Bobbioni-Harsch *et al*. [42] found no connection between the reduction in insulin resistance levels and the improvement of autonomic activity. In contrast, two studies demonstrated a positive correlation in the decrease in insulin resistance with an increase in HRV [38, 40].

Biomarkers (Leptin, GLP-1, NT-proBNP)

Only one of the two studies [40,42] that assessed Leptin identified a significant reduction at 3 ($p=<0.05$) and 12 ($p=0.003$) months after BS; for this hormone. Accompanying this, the decrease in Leptin established a positive correlation with an increase in HRV [42]. Amongst the studies included, only Gandolfini *et al.* [37] assessed the quantities of NT-proBNP. An increase in NT-proBNP was observed within the physiological range after BS and was positively correlated with HRV optimization [37]. Five of the thirteen studies stated an increase in GLP-1 secretion after BS, but all of them observed that this increase was unrelated to enhancements in HRV parameters [34,36-38,40].

DISCUSSION

This is the first systematic review that intended to explore the influence of BS and associated factors on HRV. As stated herein, it was possible to observe that:

1) the studies present heterogeneity regarding the HRV measurement intervals during follow-up after BS; 2) the equipment and duration of HRV recordings are different between studies; 3) there was an increase in parasympathetic HR control and HRV and, a decrease in HR in all BS methods undertaken; 4) the literature does not provide evidence that this effect was directly caused by the surgical procedure; 5) few studies have demonstrated that BS encouraged an earlier and more evident restoration of cardiac autonomic control in patients with TDM2; 6) the decrease in insulin resistance was correlated with the increase in HRV in some studies, but, other studies are unsupportive of these outcomes; 7) improvements in metabolic parameters (e.g., Leptin, NT-proBNP) were positively correlated with an increase in HRV.

In obese individuals, the sensitivity of adrenergic receptors is compromised, producing autonomic imbalance wherein vagal tone is reduced and sympathetic activity is increased. The increase in sympathetic tone mitigates cardiac autonomic modulation and decreases HRV [42]. The large-scale production of pro-inflammatory cytokines produced by excess adipose tissue is partly responsible for the impairment of the ANS in patients with obesity [53]. It has been demonstrated that the magnitude of inflammation assessed by biomarkers (e.g., fibrinogen, C-reactive protein, IL-6) causes impairment in vagal efferent flow and, so, is responsible for HRV decrease [54-55]. These effects were observed in young people [56], as well as in older populations with obesity [53].

Thus, weight loss occasioned after BS originates an increase in the vagal efferent flow, causing greater parasympathetic conduction and promoting an increase in HRV [41]. These effects are sturdier in obese persons who have had a weight reduction of approximately 10% [59]. In the treatment of obesity, weight loss is identified as the main cause of increased parasympathetic HR modulation [60-63] and decreased sympathetic modulation [60-61,63], since the opposite effect is observed with the gain of adipose tissue [63-64].

In our review, studies that controlled the effect of BS with non-surgical treatments did not result in significant weight loss and, consequently, did not show changes in HRV patterns. Despite this, other evidence has already elucidated that there is an increase in HRV in different types of non-surgical strategies that culminated in weight loss. Calorific restriction [59,61,66] combined or not with physical exercise [60,62], intermittent fasting [65-66] pharmacological use of absorption inhibitors [67], and even by less conventional methods such as electrical stimulation C1-C2 have reported changes in HRV after causing weight reduction [69]. These findings reinforce the evidence that the effect on HRV is totally dependent on weight loss and independent of the intervention type [59]. Yet, these interventions have been ineffective in reducing weight [29, 30], and maintaining this loss over an extensive period of time [31,32].

HRV Indexes

The majority of studies that analyzed linear indices displayed changes in HRV between 6 and 12 months after the bariatric procedure. Nonetheless, we must emphasize that these results can be offered more frequently since a smaller number of studies made other evaluations (in days and weeks) between six months.

A study directed by Alam *et al.* [43] suggested that autonomic changes could be more sensitive to identification in nonlinear indices of complexity, assuming that these components have experienced prior changes compared to linear indices. Throughout the results of this study, the Sample Entropy and the Detrended fluctuation analysis (DFA) established positive changes in the first month after BS. Still, the experimentation by

Ibacache *et al.* [46] similarly applied non-linear or complexity methods in the analysis and revealed no change in Sample Entropy in one and three months after the BS procedure.

The sympatho-vagal balance index that was supplementary in some studies, considered by the LF/HF HRV ratio, has been frequently demonstrated to be theoretically flawed and empirically unsupported. Though there are many criticisms of this measure, the most serious concern is that LF does not guide sympathetic modulation and so there is a lack of rationale (and/or convincing evidence) that its benefit regarding the HF component would index relative strength of vagal and sympathetic signaling [70-76].

The primary studies have an important restriction in that the time measurements are recorded after BS, assuming that the collection dates have a large time interval (e.g., 1 to 3 months) amid each measurement. Only Wu *et al.* [38] performed a more detailed follow-up after BS, namely, performed measurements in days, weeks and months after BS. Hence, monitoring with shorter intervals between HRV recordings could better categorize the change in autonomic behavior following BS. Hitherto, only two studies have completed nonlinear assessments and so should be further explored in subsequent investigations.

All studies that assessed the HR established a decrease after BS. These reductions in HR can be elucidated by the improvement in cardiovascular activity after BS. We emphasize that these effects are somewhat because of increased cholinergic activity on the heart and a partial blockage of adrenergic activity [77]. Relating to this, a transformation of the heart occurs, wherein there is a reversal of the ventricular mass [78-80] and a surge in the cardiovascular ejection fraction [79], lessening the requirement of the cardiac pumping frequency. Therefore, this decrease in HR is partially independent of the increase in HRV. Besides the stated issues, other metabolic factors are related to the decrease in HR. In Gandolfini *et al.* [37], a correlation was revealed between HR optimization and the obtainability of glucose, insulin resistance and GLP-1.

With the measurement of time after BS, in patients with TDM2, autonomic optimization was identified in a shorter period. Within three weeks, an increase in HRV was identified in the RMSSD, SD1, SD2 and SD1/SD2 indices [40]. In individuals without TDM2 who received RYGB, changes were only achieved in measurements taken after 3 months of surgery [40]. Casellini *et al.* [36] further identified this effect, in the comparison between groups of non-diabetics, pre-diabetics and those with TDM2; the final group being favored by BS. At 12 weeks following the intervention, a significant increase was identified in the SDNN (p=<0.005) and RMSSD (p=<0.001) indices of TDM2. For the group with pre-DM, deviations were only achieved in the 24th week in the RMSSD index (p=<0.05) and in non-diabetics, no changes were attained. This can be clarified by the positive correlation in the decrease in insulin resistance and a pronounced increase in HRV in individuals undergoing BS [38,40].

Whilst this is an interesting principle, only these two studies confirmed these results and, so, further evidence is required to provide greater support for these conclusions.

Biomarkers

Further aspects responsible for the development of complications in obese individuals established improved parameters after BS, which can have direct or indirect effect on HRV.

Amongst which, the N-terminal pro b-type natriuretic peptide (NT-proBNP) and Leptin, correlated with the progression of HRV. The increase in HR autonomic control sympathetic drive, in obese persons, is also linked to elevated Leptin levels. Lately, it has been recognized that Leptin is capable of directly stimulating hypothalamic neurons involved in the sympathetic activation network [81,82]. Similarly, its decrease triggered a diminution in sympathetic activity and, so an increase in HRV [42]. As this hormone is created in adipose cells, individuals with excess adipose tissue have a higher production of Leptin [82,84].

An increased in NT-proBNP demonstrated a significant correlation with improved HRV [85-86]. This biomarker can be adapted to classifying the degree of survival of patients with heart failure, in which values >6000mg/dl represent a severe level of disease and a reduced survival during about 90 days of evaluation [87]. In contrast, the observed improvement varied within the range of 200mg/dl. In this case, these effects are connected with an improvement in the sinus response from the properties of NT-proBNP, producing inhibition of adrenergic activity [77] and increased HRV [37].

In contrast, Glucagon-like peptide-1 (GLP-1) can be considered as independent factors, as they were unable to display correlations with HRV restoration. Insulin resistance remains a variable that has contentious results, since some studies [38, 40] correlate with increased HRV and others do not [39, 41, 42].

Perspectives

We consider BS as an effective metabolic intervention, wherein besides reducing weight (and therefore BMI), it is effective in the remission of some conditions (e.g., TDM2, Arterial hypertension, Sleep apnea) [37], but reliant on *several* metabolic characteristics enhanced by this weight reduction [36,37,39,41,42].

New studies can categorize the effects of BS in patients with specific diseases. We emphasize that this approach is proposed chiefly on the characteristics of the study population, given that some experiments have patients with different health conditions (e.g., arterial hypertension, Sleep apnea).

We recommend that HRV can be employed to evaluate cardiac autonomic control restoration after BS in obese persons. The relevance of employing HRV as an indicator of risk factors for evaluating and identifying health impairments related to autonomic function is reassuring. Our assessment elucidates the contribution of HRV analysis in detecting health changes, presenting itself as an efficient complementary assessment in the identification of health outcomes of obese patients undergoing BS. Hence, it is a tool of great clinical importance in the prognosis of BS.

CONCLUSION

In summary, we detailed suitable references that assessed HRV in subjects submitted to BS. The primary studies are unclear in the way wherein HRV data are processed. Despite this, all studies have revealed an increase in HRV after the BS procedure irrespective of the surgical method employed. There is evidence that patients with TDM2 may experience a more significant increase in HRV following surgery. Leptin and NT-pro-BNP are hormones that exhibit a correlation with the improvement of HRV after BS.

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FIGURE LEGENDS

Figure 1. Flow diagram of the Prisma protocol with search process and selection steps.

TABLE LEGENDS

Table 1. Description of the selected articles by author and year, study design, sample, age (years), BMI (kg/m²), intervention, mensuration, HRV indexes, key results and confidence interval.

Table 2. Evaluation of the Downs and Black Checklist for Quality Assessment.

Table 3. Illustration of the deviations in the follow-up period after bariatric procedure.

Table 1. Description of the selected articles by author and year, study design, sample, age (years), BMI (kg/m²), intervention, mensuration, HRV indexes, key results and confidence interval.

Author	*Study Design*	*Sample*	*Age (years)*	*BMI (kg/m²)*	*Intervention*	*Follow-Up* (After and before surgery)	**HRV indexes**	*Key results*
Lips et al.[38]	Non-randomized controlled trial	65 women: 11 Grupo controle; 27 Obesos with NGT 27 Obesos with TDM2	Control Group: 49,4±0,6 Obese NGT: 47,7± 6,4 Obese TDM2: 51,0±7.1	Control Group: 21,7±1.6 Obese NGT: 43,8±3.2 Obese TDM2: 42,0±5.5	RGB, AGB and VLCD	Preoperative Post-operative (3th week e 3 month)	Mean RR, RMSSD, SD1, SD2, SD1/SD2	RYGB and VLCD promotes optimization on control of vagal heart rhythm within 3 weeks in patients with DM2. After 3 months, the increase in HRV was evident in other groups, except in the NGT group.
Gandolfini et al.[35]	Prospective cohort study	32 women and 2 men	36 ± 11	46,3± 5,9	RGB	Preoperative Post-operative (12th month)	HR (bpm), SDNN	A significant increase was observed in the SDNN index at 12 months after surgery, indicating an improvement in HRV.
Wu et al.[36]	Prospective cohort study	9 women and 9 man	34 ± 10,2	45,4±6,8	VSG	Preoperative Post-operative (7th, 30th, 90th e 180th days)	Mean RR, SDNN, SDANN, RMSSD, pNN50, VLF, HF, LF, LF/HF, SD1 e SD2	Improvements in insulin resistance were associated with increases in the RMSSD and HF indices.
Maser et al.[37]	Prospective cohort study	29 women and 3 man	38 ± 11	51 ± 11	RGB	Preoperative Post-operative (6th month)	LF(ms²), LF(nu), HF(ms²), HF(nu), LF/HF	The induced weight loss provided an improvement in cardiac autonomic control, identified through the spectral activity of HRV indices.

Braga et al.[32]	Prospective cohort study	Medical Treatment: 16 women and 4 man Surgical Group: 14 women and 6 man	Medical Treatment: 35 ± 11,7 Surgical Group: 38,5± 10,6	Medical Treatment: 42,9± 4,7 Surgical Group: 41,5± 5,0	RGB	Preoperative Post-operative (3th month)	SDNN, RMSSD, PNN50, NN50, LF, HF, LF/HF	Three months after bariatric surgery, the increase in HRV was identified through the time domain indexes.
Lucas et al. [33]	Prospective cohort study	26 women and 2 men	*42,6± 11,6*	*44,1± 6,3*	RGB	Preoperative Post-operative (3th and 6 months)	HR(bpm), RR mean, SDNN, rMSSD, NN50, pNN50%	It was identified improving vagal cardiac control in three and six months, after a BS.
Nault et al. [44]	Non-randomized controlled trial	6 women and 4 men	Surgical Group :37,7± 8,5 Control Group: 44,7± 10,8	Surgical Group: 52,3± 7,6 Control Group: 54,3± 10,9	BPD-DS	Preoperative Post-operative (between 6th- 12th month)	HR(bpm), SDNN, SDANN, RMSSD, PNN50, LF(ms2), HF (ms2), LF/HF (ms2)	After BS there was an increase in HRV indices and a decrease in HR.
Machado et al. [43]	Prospective cohort study	42 women and 19 men	37 (18-66)	43 (37- 56)	RGB	Preoperative Post-operative (6th month)	RR, SDNN, RMSSD, PNN50%	There was an increase in HRV after surgery, both in the total variability (NN, SDNN) and in the short-term components of HRV (PNN50 and RMSSD).
Bobbioni-Harsch et al. [41]	Prospective cohort study	12 women	Operation: 39,5 ± 2 Control Group: 40,0 ± 2	Operation: 44,6 ± 1.1 Control Group: 29,7 ± 1.6	RGB	Preoperative Post-operative (3th and 12th month)	SDNN (ms), HRVi, TINN (ms), pNN50%.	Improvements in HRV indices were seen most robustly in the 12 months after surgery.

Alam et al. [42]	Prospective cohort study	8 women and 3 men	47.8±7.9	48.2±6.9	AGB, BPD	Preoperative Post-operative (1st, 6th, 12th month)	HR(bpm), RMSSD, SDNN, SampEn, DFAa-NN,	Some indexes showed changes from 1 month after the surgical procedure. In the more longitudinal analyzes, changes were seen in a greater number of indices.
Perugini et al. [40]	Prospective cohort study	21 women and 7 men	45±9.0	46±6.0	RGB	Preoperative Post-operative (2rd week e 6th month)	HR(bpm), RMSSD, SDNN, SDANN and HRVi.	HRV optimization was identified in a short period (two weeks), as well as in a period of six months after the intervention.
Casellini et al. [34]	Prospective cohort study	57 women and 13 men	Non-DM: 41.23±2.36 Pre-DM: 39.71±2.20 T2DM: 52.252±2.41	Non-DM: 46.75±1.39 Pre-DM: 46.99±1.34 T2DM: 44.18±1.52	RGB, SVG	Preoperative Post-operative (4th, 12th and 24th week)	HR(bpm),, RMSSD, SDNN	The increase in HRV after BS was more evident in patients with TDM2.
Ibacache et al.	Prospective cohort study	23 women	36.0 ± 11.1	35.1 ± 3.4	SVG	Preoperative Post-operative (1st and 3rd month)	HR(bpm), RMSSD, SDNN, PNN50, HF, LF, LF/HF, SD1, SD2 and SampEn	There was an improvement in HRV parameters at one and three months after the BS procedure.
Kokkinos et al.	Prospective cohort study	37 patients (sex non-specified)	RYGB: 38.0±7.8 SVG: 40.3±9.9	RYGB: 47.9±6.0 SVG: 51.6±7.5	RYGB, SVG	Preoperative Post-operative (3rd and 6th month)	HF, LF/ LF/HF	The RYGB and SVG procedures have the same results in the HRV parameters after the BS procedure.

AGB= Adjustable Gastric Banding; RGB= Roux-en-Y gastric by-pass; BPD= Biliopancreatic Diversion; BPD-DS= Biliopancreatic Diversion with a Duodenal Switch; VSG= Vertical Sleeve Gastrectomy; NGT= Normal glucose tolerance; TDM2= Type 2 diabetes mellitus; VLCD= Very low caloric diet; RR= RR intervals; HR= Heart Rate; bpm= Beat per minute; Min= minimum; Max= maximum; RMSSD = square root of the square mean of the differences between adjacent normal RR intervals; SDNN = standard deviation of all normal RR intervals; SDANN= standard deviation of averaged RR intervals over a 5-minute period; pNN50 = percentage of adjacent RR intervals with duration difference greater than 50ms; HRVi= triangular index calculated from the total number of all RR intervals divided by the height of the histogram of all RR intervals; TINN= Triangular Interpolation of RR intervals histogram LF = low frequency component; HF = high frequency component; VLF= very low frequency component; LF / HF = ratio between low and high frequency components; Nu: standard unit; ms^2: absolute unity; SD1: dispersion of points perpendicular to the identity line, instantaneous record of beat-to-beat variability; SD2: scatter of points along the identity line; long-term record of HRV; SampEN= Sample entropy; DFAa (NN)= Detrended fluctuation fractal analysis of NN intervals;

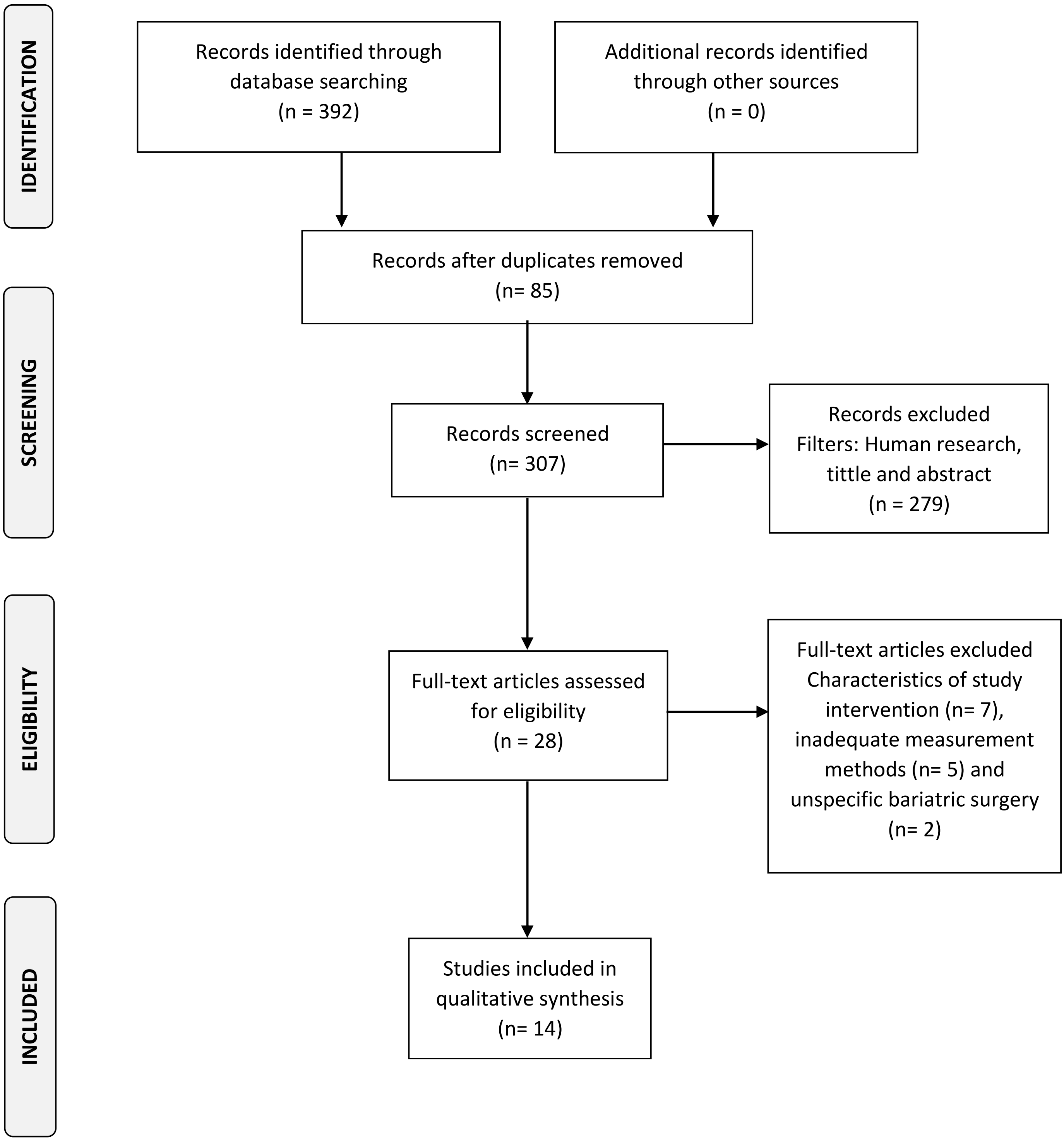
Downs & Black - Checklist Items

		Reporting	External Validity	Bias	Counfounding	Power	Quality Rating
Study	**Year**	**1 to 10**	**11 to 13**	**13 to 20**	**21 to 26**	**27**	**Total**
Lips et al.[38]	**2013**	10	2	5	3	1	**21**
Gandolfini et al.[35]	**2015**	9	2	4	3	1	**19**
Wu et al.[36]	**2014**	9	2	4	3	1	**19**
Maser et al.[37]	**2013**	8	2	4	3	1	**18**
Braga et al.[32]	**2020**	10	2	4	4	1	**21**
Lucas et al.[33]	**2020**	10	3	5	4	1	**23**
Nault et al.[44]	**2006**	9	2	5	1	1	**18**
Machado et al.[43]	**2009**	9	2	4	4	1	**20**
Bobbioni-Harsch et al.[41]	**2009**	9	2	4	3	1	**19**
Alam et al.[42]	**2009**	8	2	5	1	1	**17**
Perugini et al.[40]	**2010**	8	2	5	2	1	**18**
Casellini et al.[34]	**2016**	10	2	5	2	1	**20**
Ibacache et al.	**2020**	9	2	5	3	1	**20**
Kokkinos et al.	**2013**	9	2	4	4	1	**20**

Table 3 - Illustration of the deviations in the follow-up period after bariatric procedure.

Author	Intervention	Time Domain					Frequency Domain					Geometric Index		Poincare-Plot			Non-linear	
		RMSSD	SDNN	SDANN	PNN50	NN50	HF (ms)	LF (ms)	HF n.u)	LF (n.u)	LF/HF	HRVi	TINN	SD1	SD2	SD1/SD2	DFA	SampEn
Lips et al.[38]	RGB, AGB	↑												↑	↑	↑		
Gandolfini et al[35]	RGB		↑															
Wu et al.[36]	VSG	↑	↑	↔	↑		↑	↑			↓			↔	↔			
Maser et al.[37]	RGB						↑	↑	↔	↔	↓							
Braga et al.[32]	RGB	↑	↑		↑	↑	↔	↔			↔							
Lucas et al. [33]	RGB	↑	↔		↑	↑												
Nault et al. [44]	BPD-DS	↑	↑	↑	↑		↑	↑			↔							
Machado et al. [43]	RGB	↑	↑		↑													
Bobbioni-Harsch et al. [41]	RGB	↑	↑		↑							↑	↑					
Alam et al. [42]	AGB, BPD	↑	↑														↓	↑
Perugini et al. [40]	RGB	↑	↑	↑									↑					
Casellini et al. [34]	RGB, SVG	↑	↑															
Ibacache et al.	SVG	↑	↑		↑		↑	↑			↔			↑	↑			↔
Kokkinos et al.	RYGB, SVG						↑	↑			↔							

PRISMA 2009 Flow Diagram



- The studies present heterogeneity regarding the HRV measurement intervals during follow-up after BS;
- There was an increase in parasympathetic HR control and HRV and, a decrease in HR in all BS methods undertaken;
- The literature does not provide evidence that this effect was directly caused by the surgical procedure;
- Few studies have demonstrated that BS encouraged an earlier and more evident restoration of cardiac autonomic control in patients with TDM2;
- The decrease in insulin resistance was correlated with the increase in HRV in some studies, but, other studies are unsupportive of these outcomes;
- Improvements in metabolic parameters (e.g., Leptin, NT-proBNP) were positively correlated with an increase in HRV