Effects of weight changes in the autonomic nervous system: a systematic review protocol

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Background

The prevalence of overweight and obese individuals is increasing at an alarming rate throughout the world, in both developed and developing countries. In 2005, it was estimated that 937 million people throughout the world were overweight, and 396 million people were obese. In 2030, the respective number of overweight and obese adults was projected to be 1.35 billion and 573 million individuals.[1] Epidemiologic studies indicate that overweight and obesity are important risk factors for diabetes, cardiovascular disease, cancer and premature death.[2] The rising prevalence and the associated comorbidities will be a major expense in healthcare budgets in developed and developing countries, straining production rates and decreasing workforce vitality, capabilities and quality of life. Despite recent breakthroughs, there is still no pharmacological agent or surgical procedure widely accepted as a gold-standard therapy with intention to cure. So far, the best methods for prevention and management of excess weight and obesity are nutritionally balanced diets and exercise regimens.

The autonomic nervous system (ANS) is the visceral control system of the body, regulating blood vessel tone, heart rate, gastrointestinal function, energy metabolism and hormonal response. A 10% increase in body weight is associated with a decline in parasympathetic tone, accompanied by a rise in mean heart rate, and conversely, heart rate declines during weight reduction.[3] Reductions in vagal activity with increment in weight may be one mechanism for the arrhythmias and other cardiac abnormalities that accompany obesity.[3] Furthermore, the ANS plays an important role in metabolism, and obesity is associated with a relative or absolute reduction in the activity of the thermogenic component of the sympathetic nervous system.[3] Numerous studies have pointed out changes in ANS activity in overweight and obese test subjects, in both humans and animal test models. However, it is still a matter of controversy the physiological effect of dietary and physical activity habits. The inconsistency is thought to arise largely from the difficulty in controlling the arrangement of variables (including genetic differences, physical activity levels, the degree of obesity, dietary and behavioral habits,
and emotional stress) and in adequately assessing the SNS activity in human subjects of all age groups.[4]

Given the complexity of the ANS, there is no single test that precisely reflects function of a specific branch of this system.[5] Therefore, it is not uncommon to order numerous tests based on diverse reflexes. Traditionally, research in ANS activity was done by testing the autonomic reflexes (Valsalva manoeuvre, deep breathing, isometric handgrip test, orthostatic test, cold pressure test, among others).[5] More recently, new techniques, such as evaluation of heart rate variability, measurement of neurotransmitter levels and microneurography, have been introduced as research tools.[5, 6]

The aim of this systematic review is to understand the modulation of the activity of sympathetic and parasympathetic nervous systems induced by weight gain and loss resulting from dietary and physical exercise regimens in human subjects.

**Review questions/objectives**

**Population** – Patients who underwent weight change regimen;

**Interventions** – Diet and exercise-based interventions resulting in weight change;

**Outcomes** – HRV parameters [total power, high frequency (HF), low frequency (LF), very low frequency (VLF), normalized units of LF (LFnu) and HF (HFnu), LF/HF ratio, standard deviation of normal to normal intervals (SDNN) and root mean square of successive differences (RMSSD)], muscle sympathetic nerve activity, noradrenaline spillover rate, baroreflex sensitivity and pupillometry parameters;

**Study designs** – Randomised controlled trials (RCT) and observational studies.

**Inclusion criteria**

**Types of participants**

We will include participants of any age, gender, ethnic group or Body Mass Index (BMI). Participants with an history of acquired or inherited diseases associated with autonomic neuropathy or autonomic dysfunction [7-9] will be excluded. Specifically, cardiovascular diseases, such as hypertension [10], heart failure [11], cerebrovascular and neurological disease [12, 13], diabetes [14] and psychiatric, eating or sleep disorders. Participants who were regular smokers and under the effect of any drug that could influence directly or indirectly the ANS activity [15], will not be included in the systematic review.

**Types of intervention**

Interventions to be considered for this meta-analysis will include all diet and/or exercise-
based weight change regimens. Trials that evaluated pharmacological or surgery based interventions will be excluded, due to previous reports of autonomic dysfunction after surgery [16] and acute effects of sibutramine in the ANS [17].

**Types of outcome measure**

The primary outcome measures will be HRV parameters [total power, high frequency (HF), low frequency (LF), very low frequency (VLF), normalized units of LF (LFnu) and HF (HFnu), LF/HF ratio, standard deviation of normal to normal intervals (SDNN) and root mean square of successive differences (RMSSD)]. As secondary outcomes, muscle sympathetic nerve activity, noradrenaline spillover rate, baroreflex sensitivity and pupillometry parameters will be assessed.

**Types of studies**

This systematic review will consider randomised controlled trials (RCT) and observational studies that evaluated the effect of weight change interventions in the activity of the autonomic nervous system.

**Search strategy**

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be undertaken in this systematic review, with the following stages:

- The first stage will comprise a limited search of PubMed (1879 to the present) and CINAHL Plus with Full Text (1937 to the present) databases, with subsequent analysis of the title, abstract and index terms of the results. This will allow the identification of relevant keywords.
- The second stage will comprise an extensive search of the literature across all included databases using all identified keywords and index terms.
- The third stage will comprise a search of the reference lists and bibliographies of the articles collected in the second stage.

The initial search query included the terms “weight change” and “autonomic nervous system”. The search strategy is annexed to this protocol. Articles published in English in the last 10 years and indexed in the following databases will be considered for inclusion in this review.

The following databases will be searched in this systematic review:

- MEDLINE (1946 to the present) and other citations sources included in PubMed;
- CINAHL Plus with Full Text;
- Web of Science™ Core Collection (1900 to the present);
• Scopus (1823 to the present);

Full copies of the articles identified by the search and considered to meet the inclusion criteria based upon the title, abstract and index terms, will be obtained for data synthesis. Articles identified through reference lists and bibliography searches will be considered for inclusion in the next phase based upon their title and abstract. Two reviewers will independently select the articles that meet the inclusion criteria. Discrepancies in reviewer selections will be resolved at a meeting between reviewers prior to the extraction of the selected articles.

Data collection

Quantitative data will be extracted from studies included in the review using a data extraction sheet developed by the authors, which will include specific details about the study groups, methodology and intervention characteristics, outcomes and results. Data will be independently extracted by two reviewers (JC and DS). Measures will be taken to avoid the inclusion of duplicated studies, including comparing author names, sample sizes, intervention characteristics and outcomes. If necessary, authors will be contacted for additional information. If the data is only available in a graphical image and the quantitative data is not provided by the authors, WebPlotDigitizer software will be used for quantitative data extraction from graphics (Rohatgi A, 2017, version 3.11, Austin, TX, USA).

The following data will be extracted from each study: (1) study design (randomization, blinding), (2) characteristics of the participants (sample size, age range), (3) characteristics of the intervention and protocol (duration, diet composition and total calorie consumption, characteristics of the exercise training program), (4) weight change (presented as relative percentage of change in weight in BMI, or when not available in kg) (5) outcomes (type, characteristics of the outcome measurement conditions and main results). In case of exclusion, the justification will be based on the inclusion and exclusion criteria.

Assessment of methodological quality

Evidence will be classified per each outcome. The overall quality of evidence will be assessed using the GRADE methodology. For each outcome, quality of evidence will be classified using 5 criteria: (1) risk of bias, (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias. Quality will be considered as follows: high, if multiple RCTs with a low risk of bias have consistent, generalizable results for an outcome; moderate, if one of the criteria is not met; low, if two of the criteria are not met; and very low, if three of the criteria are not met. If just one study measuring an outcome exists, the data will be considered sparse and the corresponding evidence classified as low. GRADE profiler software (version 3.6) will be used for the analysis.

Quality of evidence reflects the extent to which the reviewers’ confidence in an estimate
of effect is adequate to support a recommendation. In the GRADE system, strength of recommendation is classified as strong or weak according to the quality of the supporting evidence and the balance between desirable and undesirable outcomes.

Data synthesis

Studies with a similar design and comparable outcomes will be selected for quantitative analysis and their results pooled using a random effect meta-analysis in Review Manager software (version 5.2). Heterogeneity will be evaluated by the I² test and risk of publication bias with funnel plot symmetry. Selective reporting bias will be accessed by comparing outcomes of interest listed in the methods of each included study with the ones presented in the results.

Potential conflicts of interest

No conflicts of interest are present.

References