Title: PREVENTING METABOLIC SYNDROME IN MORBID OBESITY WITH RESISTANCE TRAINING: REPORTING NON-RESPONDER PREVALENCE

ID: RP08042019

DATE: April 11, 2019

Study Documents

Scientific background: The prevalence of metabolic syndrome (MetS) and cardiovascular disease is expected to rise along with the global obesity epidemic [1]. MetS is a cluster of clinical risk factors, including abdominal (visceral) obesity, hypertension, elevated serum triglycerides, low serum high-density lipoprotein (HDL) and hyperglycaemia [2]. Additionally, MetS is also associated with a pro-inflammatory state that leads to an altered physiological balance of adipokines, insulin resistance, endothelial dysfunction and a pro-atherogenic state [3], that increase the cardiovascular risk when population have more fat as the obesity state [4]. The morbid obesity is considered as a chronic disease highly-related with MetS development [5]. The MetS for example, significantly decreases the life expectancy of individuals with morbid obesity [4] and increases the disease burden and economic costs associated with healthcare [6]. In this sense, more recently, there was reported that body mass index (BMI) and fat distribution showed higher associations with inflammation, fat indices, and more prevalence of MetS in morbidly obese subjects [7], claiming for an early prevention of the MetS in the morbid obese state. Exercise training has proven to be effective in inducing a clinically significant weight loss and reducing cardiovascular risk [8]. Exercise have reported to be associated with increased muscle mass, decreased body fat, and improved metabolic profile (i.e., improved glucose control and lipid levels) [9].

Additionally, exercise training in MetS patients was also associated with a significant reduction in high-sensitivity C reactive protein, and insulin resistance, but independent of weight loss [10], being this last effect (i.e., weight loss) a non-necessary aim into morbid obese patients. However, considering that the cardiorespiratory fitness (CRF) have been reported to be a strong predictor of overall health, exercise training may improve CRF in patients with MetS [11, 12], and thus we speculate that the CRF related outcomes such as the walking perform can be relevant for the health in obese patients at risk of MetS. Additionally, the resistance exercise training (RT, i.e., a particular exercise training modality consisting in stimulating muscles using external weights), may help to reduce health markers as systolic blood pressure (SBP) in obese patients with MetS risk factors [13]. In addition, supervised RT improved muscle strength and functional capacity in patients with obesity undergoing bariatric surgery [14]. However, although RT has been widely studied in obesity [15], there is little information in the morbid obesity. On the other hand, there is poor knowledge similarly, about the interindividual variability to exercise training in terms of responders and non-responders (NR). For example, as in reducing fat markers, we have shown that more baseline fat (overweight, obesity) have showed higher fat decreases and thus less NR, we speculate that morbid obese patients could decrease more both fat and MetS markers than other peers with less fat as those with obesity. Objectives: to determine the effects of a resistance training programme (RT) in preventing or attenuating metabolic syndrome (MetS) in patients with morbid obesity. A second aim was to report the prevalence of NR in terms of improvements in MetS markers and other co-variables considered. Design: An experimental, and non-randomized control clinical study. Methods: In an experimental clinical trial, obese and morbid obese patients will be invited for participaiting in a lifestyle study including resistant training during 20 weeks for preventing MetS in this cohort. Participants will be

recruited from the morbid obesity (Temuco, Chile), during two months by phone invitation. The sample size will be determined in accordance with the study's feasibility recruitment, and a previous pilot study where it was determined the effects of a RT programme on anthropometric parameters, muscle function and metabolic profile and nutritional in the potential morbid obese patients [8]. The study will be completed in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of the Universidad de La Frontera, Temuco, Chile. Patients and Recruitment: The inclusion criteria will be as follows: i) older than 18 and younger and =65 years of age (i.e., 65 y is the retirement age in women in Chile), ii) daily activities including walking, physical autonomy, iii) medical authorization by a physician, and iv) body mass index (BMI) =35 kg/m^2, according to BMI, general population is classified: class II obesity (BMI =35.0-39.9 kg/m^2), class III - extreme obesity or mobid obesity (BMI =40 kg/m^2) [16, 17]. Exclusion criteria will be: i) physical limitations (e.g., restricting injuries of the musculoskeletal system, or dependent of a third person), ii) exercise-related dyspnoea or respiratory alterations, iii) chronic heart disease with any worsening in the last month, and iv) an adherence rate of less than 80% of the total interventions (excluded from the statistical analyses).

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Statistical Analysis Plan (SAP): We will apply 2 main forms of statistical analyses a) to report the pre-post changes in mean terms, and b) to report the results according with the inter-individual responses based on the technical error criteria, where according with the error calculated in the three previous measurements registered by the sample that was voluntary. Thus, for example, we will classify the subjects in responders and non-responders by the technical error of measurement, and additionally, we will classify the subjects according with a responder and non-responder clinical criteria, where we will classify as responders to all subjects who can be able of changing an initial adverse clinical altered profile for a healthy new classification. Thus, the specific statistical methods that we hope to apply for each analysis are; test of normality and homoscedasticity assumptions using Shapiro-Wilk and Levene's tests, the Student's t test for the identification of differences at baseline. An ANCOVA will be conducted (for potential confounders outcomes) in those altered baseline differences outcomes. We also hope to apply the repeated measures of two-way (group, time) to assess occurrence of an actual training effect [i.e., $p < 0.05$ for the interaction (group × time) for the different study outcomes]. Among the specific statistical methods we hope to apply the Bonferroni post hoc test we hope to apply when we can be seen test differences among groups. Similarly, we hope to apply the Cohen's d test in order to detect effect size, using the threshold values of 0.20, 0.60, 1.2, and 2.0 for small, moderate, large, and very large effects, respectively [18], with 95% confidence intervals (CI). The alpha level was fixed at $P<0.05$ for statistical significance.