Addressing the problem of weight regain after caloric restriction in people with obesity: new therapeutic approaches and potential mechanisms (REGANE)

Synopsis/Abstract (max 800 words)

Obesity is a chronic disease affecting millions of people worldwide, often accompanied by an increased risk of other chronic diseases and poor quality of life. Maintaining a 5-15% reduction of body weight considerably improves the health prognosis of patients with obesity. This reduction can be achieved by most patients by restricting food intake. However, 30-50% of the lost weight is typically regained within the first year after weight loss behavioral therapy and at least 50% of patients regain their initial weight within 5 years. Increased appetite and reduced total energy expenditure following weight loss have been portraited as the main mechanisms underlying this weight loss regain. Rapid weight regain also occurs with the newer generation of highly effective anti-obesity medications upon treatment discontinuation. Therefore, regaining weight after successful weight loss interventions represents a major challenge in the treatment of obesity. In this research project, the problem of weight regain in people with obesity will be addressed, in 2 studies, by exploring a new therapeutic approach (time-restricted eating) and a new potential mechanism (organ-specific adaptive thermogenesis).

Time-restricted eating (TRE) has emerged as a very promising strategy for treating obesity. TRE is a form of intermittent fasting that consists of confining all daily meals to a time period of 4-10 hours, while fasting for the rest of the day. TRE induces spontaneous weight loss and improves cardiometabolic health, but its effect on body weight does not appear to exceed that of calorie restriction. Paradoxically, TRE has been shown to increase satiety and improve appetite regulation. These findings, together with the behavioral constraints imposed by confining all meals to a short period of time, suggest that TRE might be an effective strategy to combat the hyperphagic response that drives weight regain after diet-induced weight loss, ultimately promoting weight loss maintenance. For testing this hypothesis, we are going to conduct a randomized controlled trial in which 212 patients with obesity will be randomized to a control group (having at least 12h between the first and last daily meal) or a TRE group (eating all meals within 8h/day). Both groups will go through a tightly controlled calorie restriction intervention (with or without TRE) for 12-16 weeks until they lose 8-10% of their body weight. Then, the calorie restriction intervention will be stopped but patients will still receive behavioral counselling for maintaining their eating window (+12 or -8 h/day) for 12 months, with the first 6 months receiving intensive behavioral support. The primary outcome is the change in body weight during the 6 months following the weight loss intervention. Secondary outcomes include body composition; body weight and eating window at the end of the follow-up period; resting, postprandial and activity energy expenditure (EE); appetite regulation and energy intake; and cardiometabolic risk factors.

This large RCT, including an extensive physiological phenotyping, will allow us to address two important secondary aims. On the one hand, we will have the opportunity to test whether TRE does confer weight loss-independent metabolic benefits, a matter that is still a subject of intense debate. On the other hand, by conducting prospective observational analyses, we will aim to identify predictors of weight regain, which might serve to unravel part of the still partially unknown physiology of the weight-reduced state.

Adaptive thermogenesis (AT), a decrease in EE exceeding what can be attributed to the changes in body weight and composition, has been for long hypothesized to mediate weight regain. However, recent studies have failed to observe an association between AT and weight regain. Crucially, to date,

AT has been investigated by measuring whole-body EE. This leaves a critical gap in knowledge regarding organ-specific AT. It is plausible that different organs exhibit varying degrees of AT, with some potentially lacking AT altogether. If this hypothesis was confirmed, it could explain the aforementioned lack of association. Despite the in vivo measurement of organ-specific EE has traditionally been unfeasible in humans, recent advancements in medical imaging, such as positron emission tomography, offer an unprecedented opportunity to study organ-specific EE. We are going to conduct some pilot RCTs in which, for the first time in humans, organ-specific EE will be measured in patients with obesity before and after an 8-10% weight loss diet intervention or a no weight loss period. That will allow us to explore whether organ-specific AT, unlike whole-body AT, is associated with weight regain.

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Proposed list of secondments (not mandatory, but recommended if known already):

Centro de Investigaciones Médico-Sanitarias, Universidad de Málaga (Spain)
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Main ArchiFun theme involved:

Translational research in prevalent diseases