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Association between circulating irisin levels and the promotion of insulin resistance during the weight maintenance period after a dietary weight-lowering program in obese patients

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ABSTRACT

Objective. Weight regain is associated with the promotion of insulin resistance. The newly discovered myokine irisin, which was proposed to be involved in the management of insulin sensitivity, could play a role in this process. This study aimed to investigate the association between irisin and reduced insulin sensitivity induced by weight regain.

Materials/Methods. Insulin sensitivity was evaluated according to the homeostasis model assessment of insulin resistance (HOMA-IR) in 136 obese patients who followed an eight-week hypocaloric diet (30% reduced energy expenditure) to lose weight and was re-evaluated four or six months after treatment. Irisin plasma levels, as well as the levels of leptin, adiponectin, ghrelin and TNF-α, were quantified in a sub-cohort (n = 73) from the initially studied patients at baseline (T0), at the diet endpoint (T1) and after the follow-up period (T2).

Results. After a successful dietary intervention to lose weight, 50% of the patients who regained the lost weight during the follow-up period were categorized as insulin resistant (HOMA-IR ≥ 2.5) compared with only 25% of patients who maintained the weight loss (p =0.018). Importantly, in addition to the well-studied hormones leptin and adiponectin, irisin plasma levels were statistically associated with several risk factors for insulin resistance. Indeed, the increased risk of insulin resistance during the follow-up period was related to high irisin levels at baseline (odds ratio = 4.2; p = 0.039).

Conclusions. Circulating irisin predicts the insulin resistance onset in association with weight regain. Therefore, irisin could be secreted as an adaptive response to counteract the deleterious effect of excess adiposity on glucose homeostasis.

Abbreviations: AHEAD, Action for Health Diabetes; BMI, Body mass index; FNDC5, Fibronectin type III domain-containing 5; HOMA-IR, Homeostasis assessment model of insulin resistance; RESMENA-S, MEtabolic Syndrome REduction in Navarra Study; TNF-α, Tumor Necrosis Factor-alpha; WAT, White adipose tissue.

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1. Introduction

Nutritional interventions, such as caloric restriction diets, are currently the most suitable noninvasive therapeutic approach to promote weight loss in the obese patients [1]. Most therapeutic trials involving dietary treatments report mean weight losses greater than 5% of body weight [1]. In addition to reducing body weight, dietary treatments are able to counteract comorbidities of obesity, including insulin resistance. However, long-term data regarding the effect of dietary interventions on mortality are disappointed, as was recently determined by the Look AHEAD (Action for Health Diabetes) study [2]. This fact could be because less than 20% of individuals who attempt to lose weight are able to achieve and maintain a 10% reduction over a year [3]. This adverse dietary outcome has relevant health consequences because weight regain may contribute to all-cause mortality [4].

Importantly, it was recently proposed that the deleterious metabolic features associated with excess body weight are largely related to the presence of insulin resistance [5] because it is associated with obesity and may increase the risk of all-cause, cancer, and cardiovascular disease mortality [6,7]. Therefore, research examining the detrimental effects of weight regain on insulin sensitivity to elucidate the potential mechanisms involved in this process is an important priority to develop more personalized therapeutic approaches to counteract obesity and its comorbidities.

Insulin resistance is a pathological condition characterized by a decrease in the efficiency of insulin to regulate blood sugar levels that occurs in response to a complex interplay of metabolic and inflammatory mediators of energy balance. In addition to well-studied energy metabolism and insulin resistance-related proteins, such as leptin, adiponectin, ghrelin and tumor necrosis alpha [8], an exercise-induced peptide known as irisin has recently been identified [9]. Relevantly, irisin was reported to improve obesity states and glucose homeostasis and to prolong life expectancy [9]. This protein was initially described as a cleavage product of the type I membrane protein fibronectin type III domain-containing 5 (FNDC5) [9]; however, recent crystal structure and biochemical characterization studies of the FNDC5 ectodomain corresponding to the irisin myokine, indicated that irisin consists of an N-terminal fibronectin III(FNIII)-like domain attached to a flexible C-terminal able to form dimers independently of glycosylation [10].

Since its discovery, irisin garnered great attention as it was noted that this peptide could play an important role in animal and human physiology and biology [11]. Nevertheless, the beneficial role attributed to irisin in humans is unclear [12], and the effects of exercise training on FNDC5 gene expression and irisin levels remain unspecified [9,13–18].

Although irisin was initially described as an exercise-induced hormone secreted by muscle [9], and it was found related to other myokines [19], it was also described to behave as an adipokine expressed and secreted by white adipose tissue (WAT). In particular the secretion of irisin mainly by subcutaneous adipocytes in rats and humans depending on exercise and nutritional status had been reported [20]. In addition, it was found that irisin is expressed in glutamate decarboxylase-positive Purkinje cells of the cerebellum in the brain [21], and an important role in the neurogenic regulation was suggested [22,23]. Interestingly, it appears to have no in vitro effect on cell proliferation and malignant potential of obesity-related cancer cell lines in physiological and higher physiological/pharmacological concentrations [24]. Moreover, this peptide could influence the regulation of metabolic pathways, and the postnatal growth and development of different organs in the newborn because it is present in human breast milk [25].

Lower circulating irisin was associated with the onset of type 2 diabetes [26–28] with the risk of non-alcoholic fatty liver disease [29], chronic kidney disease [30] and heart failure [31]. Additionally, oxidative stress and inflammation, which are two mechanisms involved in the onset of insulin resistance [32], were associated with an increase in irisin levels, as was reflected in human muscle [33] and liver [34]. However, the irisin effect appears to be exerted in a nutrition-independent fashion because its circulating levels were not associated with dietary indices [35].

The goals of this study were to evaluate the impact of weight regain after a successful hypocaloric diet-induced weight loss on the prevalence of insulin resistance classified according to the homeostasis assessment model of insulin resistance (HOMA-IR) and to explore the association among circulating levels of irisin and the detrimental effect of weight regain on insulin sensitivity, as well as changes in hormones that can affect insulin resistance such as leptin, adiponectin, ghrelin and tumor necrosis factor-alpha (TNFα).

2. Patients and Methods

2.1. Study patients and design

The study protocol included a group of obese patients (n = 136; body mass index 33.3 ± 4.4 kg/m^2; 74 men/62 women; 43.0 ± 11.2 years) who followed an eight-week hypocaloric diet (−30% energy expenditure) to lose weight and who were re-evaluated four or six months after treatment (Fig. 1). The therapy program was based on a nutritional intervention controlled by trained dieticians from the Department of Nutrition, Food Sciences and Physiology of the University of Navarra.

Among the total participants, 63 patients (cohort 1; 32 men/31 women) were enrolled in a nutritional weight loss program that consisted of an eight-week balanced hypocaloric diet containing 55% of the energy supply as carbohydrates, 15% as proteins, and 30% as fat. Upon completion of the dietary intervention (week 8; T1), volunteers were given general dietary guidelines to maintain the weight loss but without calorie restrictions or specific follow-up instructions. Six months after dieting ended (week 32; T2), the patients returned to the clinical research unit for further assessment.

The additional 73 participants (cohort 2; 42 men/31 women) followed a therapy program based on the RESMENA-S (MEtabolic Syndrome REduction in Navarra) study, which was a randomized controlled intervention trial aiming to improve clinical criteria and biomarkers associated with metabolic syndrome (Met Synd) through a dietary