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Different protein composition of low-calorie diet differently impacts adipokine profile irrespective of weight loss in overweight and obese women

R. Mateo-Gallego [a,*], I. Lamiquiz-Moneo [a], S. Perez-Calahorra [a], V. Marco-Benedí [a], A.M. Bea [a], L. Baila-Rueda [a], M. Laclaustra [a], J.L. Peñalvo [b], F. Civeira [a], A. Cenarro [a]

[a] Unidad Clínica y de Investigación en Lípidos y Arteriosclerosis, Hospital Universitario Miguel Servet, Instituto de Investigación Sanitaria Aragón (IIS Aragón), Universidad de Zaragoza, CIBERCV, Zaragoza, Spain
[b] Tufts Friedman School of Nutrition Science & Policy, Boston, MA, USA

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Abstract *Background and aims:* High-protein (HP) diets have shown benefits in cardiometabolic markers such as insulin or triglycerides but the responsible mechanisms are not known. We aimed to assess the effect of three energy-restricted diets with different protein contents (20%, 27%, and 35%; ~80% coming from animal source) on plasma adipokine concentration and its association with changes in cardiometabolic markers.
Methods: Seventy-six women (BMI 32.8 ± 2.93) were randomized to one of three calorie-reduced diets, with protein, 20%, 27%, or 35%; carbohydrates, 50%, 43%, or 35%; and fat, 30%, for 3 months. Plasma adipokine (leptin, resistin, adiponectin, and retinol-binding protein 4; RBP4) levels were assessed.
Results: After 3 months, leptin concentration decreased in all groups without differences among them, while resistin levels remained unchanged. Adiponectin concentration heterogeneously changed in all groups (P for trend = 0.165) and resistin concentration did not significantly change. RPB4 significantly decreased by −17.5% (−31.7, −3.22) in 35%-protein diet (P for trend = 0.024 among diets). Triglycerides improved in women following the 35%-protein diet regardless of weight loss; RBP4 variation significantly influenced triglyceride concentration change by 24.9% and 25.9% when comparing 27%- and 35%- with 20%-protein diet, respectively.
Conclusions: A 35%-protein diet induced a decrease in RBP4 regardless of weight loss, which was directly associated with triglyceride concentration improvement. These findings suggest that HP diets improve the cardiometabolic profile, at least in part, through changes in adipokine secretion. Whether this beneficial effect of HP diet is due to improvements in hepatic or adipose tissue functionality should be elucidated.
Clinical trial registration: The clinical trial has been registered in ClinicalTrials.gov (Identifier: NCT02160496).

Abbreviations: AgRP, Agouti-related peptide; BMI, Body mass index; CRP, C-reactive protein; GGT, Gamma-glutamyl transpeptidase; GPT, Glutamic-pyruvic transaminase; HbA1c, Glycated hemoglobin; HP, High protein; NPY, Neuropeptide Y; RBP4, Retinol-binding protein 4.

* Corresponding author. Unidad Clínica y de Investigación en Lípidos y Arteriosclerosis, Hospital Universitario Miguel Servet, Av. Isabel La Católica, 1-3, 50009 Zaragoza, Spain. Fax: +34 976369985.
E-mail address: mateo@iisaragon.es (R. Mateo-Gallego).

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Introduction

Obesity has become a major global health problem because it reduces life expectancy, entails an important socioeconomic impact, and is strongly associated with a number of comorbidities including metabolic syndrome, type 2 diabetes, and cardiovascular disease [1,2]. Overweight and obesity are associated with excess fat mass and adipocyte dysfunction [3]. The adipose tissue plays a key role in the regulation of energy metabolism and lipid and glucose blood homeostasis through its ability to secrete numerous proteins collectively known as adipokines [4,5]. The metabolic abnormalities induced by excess weight are highly associated with peripheral insulin resistance and excessive release of free fatty acids from adipocytes, and both these processes are considered markers of adipose tissue dysfunction [4,6,7]. Altered secretion of adipokines is a consequence of adipose tissue dysfunction and is a potent mediator of the inflammatory state and metabolic disorders associated with obesity [5–8].

Recent evidence showed that energy-restricted high-protein (HP) diets induce remarkable weight loss and result in a greater improvement of cardiometabolic parameters such as insulin sensitivity, plasma triglyceride, or HDL cholesterol levels when compared with carbohydrate-dense hypocaloric diets [9,10]. Hence, HP hypocaloric diets have been proposed as a potential approach in the treatment of type 2 diabetes [11,12]. In this line, our previous work demonstrated that an energy-restricted diet with 35% of calories from proteins more effectively improved the metabolic abnormalities associated with obesity in comparison with an energy-restricted diet that is low in protein content, independently of weight loss [10]. However, the mechanisms responsible for these differential effects of HP diets are unknown. Low-calorie HP diets tend to preserve fat-free mass and achieve higher fat mass reduction, and this mechanism has been proposed as a potential driver of their beneficial effects on lipids concentration or insulin resistance [13,14]. However, other studies could not confirm this mechanism as plausible [15]. Improvement in functionality rather than depletion in adipose tissue is a reasonable hypothesis that has been proposed too [4,5]. Some recently reviewed studies have described an increase in adiponectin and a decrease in RPB4 concentrations after weight loss, which have been related to glucose metabolism improvement [16]. However, few studies have explored the effect of HP diets on adipokine concentration by showing divergent effects among different cytokines. In addition to protein quantity, the source and quality of protein could play an essential role in its beneficial effects on metabolism. Animal protein consumption is associated with cardiometabolic parameter benefits, mainly in insulin resistance, blood pressure, or adiposity-related metabolites, among others [17–19].

Thus, we aimed to explore the relation between weight loss and plasma adipokine concentration associated with different adipose tissue functions and whether energy-restricted HP diets (80% of whom coming from lean animal protein) could induce further improvement in adipose tissue functionality beyond weight loss, which could be postulated as a mechanism responsible for the cardiometabolic benefits of HP diets associated with weight loss.

Methods

Study population

The study protocol has been previously described elsewhere [10]. Briefly, women were recruited to participate in a 3-month weight loss intervention study that was carried out at a University Hospital in northern Spain. Only women were selected to homogenize the study findings. Other inclusion criteria included age 18–80 years, body mass index (BMI) 27.5–45 kg/m^2, and stable weight (±3 kg) in the previous 3 months. The exclusion criteria included hypothyroidism, uncontrolled type-2 diabetes (glycated hemoglobin (HbA1c) > 8%), any other disease that could interfere with the ability to comply with the study protocol, and current lipid-lowering or anti-diabetic drugs. Women taking supplements of phytosterols, omega-3 fatty acids, or any obesity drug were also excluded. Among participants meeting the study inclusion criteria, 91 women were randomly selected for randomization to one of three diets. A total of 80 women completed the 3-month dietary intervention period.

All subjects provided written informed consent to participate in the study. The study protocol was approved by the ethical committee of our institution (Comité de Ética e Investigación Clínica de Aragón); all procedures were in accordance with the ethical standards of that committee. This clinical trial was registered at ClinicalTrials.gov under identifier NCT02160496.

Study design

The study consisted of a 3-month weight loss intervention phase, which has been previously explained in detail [10]. We selected a 3-month period of time according to previous findings of weight loss effect on adipokine concentrations and considering that diet-induced cardiometabolic parameter changes stabilize in <4 weeks [16,20]. Intervention included individual consultations to reinforce messages and motivate weight loss. Clinical, anthropometric, dietary, and biochemical variables were assessed at baseline and after 3 months of dietary intervention.

The study consisted of a three-arm design, with subjects randomly assigned to one of three energy-reduced diets: 20%, 27%, or 35% protein. The rest of macronutrients were distributed as follows: protein, 20%, 27%, or 35%; carbohydrates, 50%, 43%, or 35%, respectively; and fat, 30% in all diets. Once all screening visits were concluded, all subject data were recorded in a data file. The first woman to be included in the study was allocated to the 20%-protein diet, the second to the 27%-protein diet, the third to the 35%-protein diet, and so on. Participants were blinded to their assigned macronutrient composition. Low-calorie diets involved a caloric restriction of 600 kcal per day, which was applied to total daily energy expenditure energy intakes. They were

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