ACYL-CoA synthetase long-chain 5 polymorphism is associated with weight loss and metabolic changes in response to a partial meal-replacement hypocaloric diet

**Abstract**

**Background:** we hypothesize that the acyl CoA synthetase 5 (ACSL5) genotype may influence weight loss secondary to energy restriction.

**Aims:** the aim of our study was to analyze the effects of the rs2419621 genetic variant of the ACSL5 gene on weight change and metabolic parameters after a partial meal-replacement hypocaloric diet.

**Methods:** this was a non-randomized, single-treatment study with a formula diet in 44 obese subjects with body mass index (BMI) greater than 35 kg/m². Patients received nutritional education and a modified diet with two intakes of a normocaloric hypoproteic formula during 3 months.

**Anthropometric parameters and biochemical profile were measured at baseline and after 3 months. The rs2419621 variant of the ACSL5 gene was assessed using real-time polymerase chain reaction.**

**Results:** T-allele carriers showed greater improvement in body weight (CC vs. CT + TT; -7.4 ± 2.1 kg vs. -9.3 ± 1.8 kg; p = 0.01), body mass index (3.1 ± 0.4 kg/m² vs. -3.4 ± 0.5 kg/m²; p = 0.02), fat mass (-5.2 ± 1.4 kg vs. -6.4 ± 1.2 kg; p = 0.01) and waist circumference (6.1 ± 1.1 cm vs. -8.6 ± 0.8 cm; p = 0.02) than non-T-allele carriers. Only subjects with the T allele showed significant improvement in triglyceride levels (-4.6 ± 2.4 mg/dL vs. -14.4 ± 2.3 mg/dL; p = 0.01). Finally, improvements in insulin (2.0 ± 0.3 mU/L vs. -4.5 ± 0.5 mU/L; p = 0.01) and HOMA-IR (0.4 ± 0.2 units vs. -1.3 ± 0.3 units; p = 0.02) were higher in T-allele carriers than in non-T-allele carriers.

**Conclusions:** our data suggest that the genetic variant (rs2419621) of the ACSL5 gene is associated with diet response after a partial-meal replacement intervention, with greater improvements in adiposity and biochemical parameters in subjects with the T allele.

**Keywords:** ACSL5, Hypocaloric diet, Meal replacement. rs2419621, Weight loss.
INTRODUCTION

Obesity is a growing global health pandemic. This disease is one of the main causes of mortality and morbidity, including cardiovascular and cerebrovascular disease, diabetes mellitus, musculoskeletal disorders, and cancer. According to the latest studies, the prevalence of obesity in the world was 12 % (1), while in Spain it was 22 % (2). For obese individuals, even a relatively small amount of weight loss may reduce the risk of developing such morbidities. The cornerstone of all treatment options for obese patients includes a reduced calorie diet and exercise, with the goal of achieving a clinically meaningful weight loss of at least 5-10 % in a 3- or 6-month period. There is evidence that partial meal replacements (MRs) are effective in inducing weight loss. Heymsfield (3) conducted a meta-analysis comparing partial replacement programs to traditional energy-restricted food-based diets, and found that MRs resulted in a 7 % loss in body weight at 3 months, compared to 3 % in the case of traditional diets.

Moreover, weight loss in response to these different caloric restriction approaches shows significant interindividual variability (4). The genes implied in fatty acid (FA) partitioning are strong candidates to play a role in weight loss. Acyl-CoA synthetases (ACSL) are involved in the supply of FAs by catalyzing the activation step of FA metabolism. Due to its location in the inner mitochondrial membrane of liver cells, the ACSL5 isoform is implied in the provision of acyl-CoA for mitochondrial oxidation (5). Because the ability to increase or maintain FA transport capacity may be a determining factor in the success of weight reduction, and ACSL5 has been demonstrated to increase with food deprivation in rats (6), we thought that the ACSL5 genotype might influence weight loss secondary to different energy-restriction strategies. Previous work (7-8) illustrated that the rs2419621 genetic variant of the ACSL5 gene (C to T transition) is associated with increased rates of weight and fat loss in overweight and obese subjects who underwent a hypocaloric diet.

The aim of our study was to analyze the effects of the rs2419821 genetic variant of the ACSL5 gene on weight loss and metabolic parameters after a partial meal replacement hypocaloric diet.

METHODS

STUDY DESIGN

The study was carried out from January 2017 to July 2019. This interventional study was approved by our Ethics Committee (UCV Committee 06/2017) and was also in accordance with the guidelines laid down in the Declaration of Helsinki. All participants provided their informed consent to a protocol approved by the local ethical review committee. This was a non-randomized, single-treatment study with a partial meal-replacement hypocaloric diet with a normocaloric hyperproteic formula (Table I). The recruitment of 44 obese patients was conducted using a consecutive method of sampling among subjects referred from Primary Care. Obese subjects were eligible to participate if they met the required criteria, including body mass index (BMI) greater than 35 kg/m² and age between 30 and 75 years. Exclusion criteria included the following: history of thyroid disease, heart attack, stroke, severe renal or hepatic disorders, active alcoholism, malignant tumor, and receiving medications known to influence lipid levels (hormonal therapy, glucocorticoids, anti-inflammatory drugs) or glucose levels (sulfonylureas, thiazolidinediones, insulin, GLP-1 receptor antagonists, S-GLT2, DPP-IV inhibitors, metformin) within 3 months before the study.

The primary endpoint was body weight loss after 3 months versus baseline. The secondary endpoints were changes in lipid profile, insulin levels, and insulin resistance. All anthropometric parameters (weight, height, body mass index (BMI), waist circumference, fat mass by impedance) and blood pressure were recorded at baseline and after 3 months. Blood samples were collected in EDTA-treated and plain tubes after a 12-hour overnight fast for the analysis of insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels. The variant of the ACSL5 gene was assessed using a polymerase chain reaction.

THERAPEUTIC INTERVENTION

After the inclusion of a patient in the study, a nutritional assessment and an analysis of biochemical markers were carried out. Patients received nutritional education and a normocaloric hyperproteic formula diet. The nutritional characteristics of the diet are shown in table I. This dietary intervention was structured into 5 meals (breakfast, morning snack, lunch, afternoon snack, dinner). Lunch and dinner were replaced by an artificial nutritional preparation (VEGEStart Complete®), whose nutritional characteristics are described in table I (normocaloric hyperproteic formula). A dietitian provided reinforcement by telephone every seven days. The different assessments and tests were carried out before the start of the dietary intervention and at 3 months after the beginning of the intervention.

ANTHROPOMETRIC PARAMETERS AND BLOOD PRESSURE

Weight was measured without clothing, with an accuracy of ± 0.1 kg, using a manual scale (Seca, Birmingham, United Kingdom). The height was measured with the patient in an upright position to the nearest centimetre, using a stadiometer (Seca Birmingham, United Kingdom). BMI was calculated using the formula: Weight (kg) / Height x Height (m²). The difference in relative weight was determined using the percentage of weight loss (%PP): (Weight before dietary intervention - Weight after dietary intervention (kg) / Initial weight (kg)) x 100. Waist circumference was determined in the narrowest diameter between the xiphoid process and iliac crest. A bioelectrical impedance analysis (BIA) (BIA 101, EFG, Akern, Firenze, Italy) was conducted in all subjects.
The BIA was performed on all subjects after fasting for at least 8 hours, and subjects were instructed not to exercise or drink alcohol within 48 hours prior to the test. An alternating current of 0.8 mA at 50 kHz produced by a calibrated signal generator (EFG, Akern, Firenze, Italy) was used and applied to the skin by adhesive electrodes placed on the back of a hand and the right foot. The parameter analyzed with the BIA was total fat mass (kg) (9).

Blood pressure was measured twice after a 10-minutes rest with a random zero mercury sphygmomanometer, and then averaged (Omrom, LA, CA, USA).

### BIOCHEMICAL AND GENETIC VARIABLES

Serum total cholesterol and triglyceride concentrations were determined by an enzymatic colorimetric technique (Technicon Instruments, Ltd., New York, N.Y., USA). HDL cholesterol was determined enzymatically in the supernatant after precipitation of other lipoproteins with dextran sulphate-magnesium. LDL cholesterol was calculated using Friedewald's formula (LDL cholesterol = total cholesterol - HDL cholesterol - triglycerides / 5) (10). Insulin was analyzed by radio-immunoassays (RIA Diagnostic Corporation, Los Angeles, CA, USA) with a sensitivity of 0.5 mIU/L (normal range, 0.5-30 mIU/L) (11); plasma glucose levels were determined by using an automated glucose oxidase method (Gluco Analyser 2, Beckman Instruments, Fullerton, California, USA), and the homeostasis model of assessment for insulin resistance (HOMA-IR) was obtained using these values (12).

Genotyping (rs241926) was performed by using customized assays with the TaqMan® OpenArray™ Genotyping platform (Thermofisher, Pittsburg, Pens, USA). Samples were loaded using the AccuFill system, and amplification performed on the QuantStudio 12K Flex Real-Time qPCR instrument (Thermofisher, Pittsburg, Pens, USA). A total sample volume of 5 μl with 2.5 μl of TaqMan OpenArray Master Mix (Applied Biosystems, Foster City, CA, USA) and 2.5 μl of human DNA was loaded and amplified on arrays following the manufacturer’s instructions. Genotype calling and sample clustering for the OpenArray assays was performed in a TaqMan Genotyper (LifeTechnologies, Carlsbad, CA, USA).

### DIETARY INTERVENTION

All patients completed a dietary record of 72 hours to assess the intake of calories and macronutrients. This record was carried out before starting the intervention. A new dietary record was done at 3 months to assess the adherence to formula-diet. The records were reviewed by a dietitian and analyzed by the program (Dietsource®, Nestlé, Geneve, Switzerland). National composition food tables were used as reference (13). The exercise recommendations for patients of both groups were the completion of aerobic physical activities at least 3 times per week (1 hour each). The exercises indicated by the authors were walking, running, cycling, swimming and muscular strength exercises (weight training or weightlifting) were contraindicated. Patients exercise activity was self-reported through a questionnaire.

### STATISTICAL ANALYSIS

The genotype distribution was tested for deviation from the Hardy-Weinberg equilibrium by a chi-squared test with 1 df ($p > 0.05$). The variant of the ACSL-5 gene was in Hardy Weinberg equilibrium ($p = 0.27$). Sample size was calculated to detect differences over 7 kg in body weight loss with 90% power and 5% significance ($n = 40$). Each variable was examined for normality with the Kolmogorov–Smirnov test. For descriptive purposes, results were expressed as average +/- standard deviation. In within-group comparisons we conducted paired t-tests for biochemical parameters at baseline and after caloric restriction. In between-group comparisons, an independent t-test was used to compare differences between both times. Non-parametric variables were analyzed with the Mann-Whitney U-test. Categorical variables were analyzed with the chi-squared test, with Yates correction as necessary, and Fisher’s test. The statistical analysis to evaluate the gene/diet interaction was an univariate analysis of covariance (ANCOVA) with Bonferroni’s test post-hoc. A chi-squared test was used to evaluate categorical parameters. The statistical analysis was performed for the combined CT and TT as a group, and for the CC genotype as a second group (wild type genotype), with a dominant model. A $p$-value < 0.05 was
considered significant. The statistical analysis was carried out with the SPSS version 19.0 software (Chicago, IL. USA).

RESULTS

We enrolled 44 subjects with obesity (29 CC (65.9 %), 13 CT (29.5 %) and 2 TT (4.5 %)). All patients completed the 3-month follow-up period without dropouts, and no adverse symptoms related to the intervention were reported. The mean age of all the group was 64.2 ± 7.3 years (range: 33-72 years) and the mean BMI 38.2 ± 2.5 kg/m² (range: 35.2-44.3 kg/m²). Sex distribution was: 34 women (77.3 %) and 10 men (22.7 %). Age was similar in both genotype groups (wild type (CC) vs. mutant type (CT + TT)) (64.5 ± 7.2 years vs. 63.9 ± 6.0 years: ns). Sex distribution was similar in both genotype groups: males (23.1 % vs. 22.5 %) and females (76.9 % vs. 77.5 %).

In these obese subjects treated with a partial-meal replacement hypocaloric diet, the baseline evaluation of dietary intakes with a 3-day written food record showed the next data: calorie intake of 1,611.8 ± 531.8 kcal/day, carbohydrate intake of 159.1 ± 63.9 g/day (39.4 % of calories), fat intake of 66.4 ± 29.3 g/day (37.1 % of calories), protein intake of 78.4 ± 22.1 g/day (23.5 % of calories), and dietary fibre intake of 15.8 ± 7.1 g/day. After 3 months of dietary intervention, these obese subjects reached the recommendations of partial-meal replacement hypocaloric diet: 1,069.9 calories per day, 150.1 ± 43.1 g/day of carbohydrates (64.4 % of calories), 27.7 ± 12.3 g/day of lipids (23.1 % of calories), 62.1 ± 12.1 g/day of proteins (23.5 %. of calories) and dietary fibre 18.3 ± 3.1 g/day. The distribution of fat was: 32.9 % of saturated fat, 50.1 % of monounsaturated fat, and 17.0 % of polyunsaturated fat. Physical activity was similar in both genotype groups (123.2 ± 27.3 min/week vs. 129.1 ± 28.2 min/week: p = 0.51).

As reported in table II, there were no significant genotype related differences (baseline and after dietary intervention) in anthropometric parameters and blood pressure. After the partial-meal replacement hypocaloric diet, body weight, body mass index (BMI), fat mass, waist circumference and blood pressure decreased. The percentage of weight reduction at 3 months was 7.2 % (5.2-9.8 %) in non-T allele carriers, with a greater weight loss at 3 months with a percentage of 9.2 % (6.1-11.2 %) in T allele carriers. T allele carriers (CC vs. CT + TT) showed greater improvement in body weight (-7.4 ± 2.1 kg vs. -9.3 ± 1.8 kg: p = 0.01),

| Parameters       | n = 44 | CC (n = 29) | CT + TT (n = 15) | p   | Time | Genotype | Genotype x time | p   | Time | Genotype | Genotype x time |
|------------------|--------|-------------|------------------|-----|------|----------|-----------------|-----|------|----------|-----------------|
| BMI              |        | Baseline    | 3 months         |     |      |          |                 |     |      |          |                 |
|                  |        | 38.2 ± 2.2  | 35.1 ± 4.1*      | p = 0.006 | p = 0.41 | p = 0.02 |                   |     | 38.1 ± 2.3 | 34.7 ± 2.1* | p = 0.004 | p = 0.32 | p = 0.01 |
| Weight (kg)      |        | Baseline    | 3 months         |     |      |          |                 |     |      |          |                 |
|                  |        | 101.7 ± 9.5 | 94.3 ± 9.1*      | p = 0.005 | p = 0.41 | p = 0.01 |                   |     | 100.4 ± 13.1 | 91.1 ± 9.1* | p = 0.001 | p = 0.35 | p = 0.004 |
| Fat mass (kg)    |        | Baseline    | 3 months         |     |      |          |                 |     |      |          |                 |
|                  |        | 44.6 ± 5.2  | 39.3 ± 8.0*      | p = 0.005 | p = 0.51 | p = 0.002 |                   |     | 43.5 ± 5.0  | 37.1 ± 6.1* | p = 0.004 | p = 0.46 | p = 0.001 |
| WC (cm)          |        | Baseline    | 3 months         |     |      |          |                 |     |      |          |                 |
|                  |        | 113.3 ± 9.1 | 106.2 ± 8.0*     | p = 0.03 | p = 0.59 | p = 0.02 |                   |     | 117.2 ± 7.1 | 108.7 ± 5.0* | p = 0.02 | p = 0.54 | p = 0.01 |
| SBP (mmHg)       |        | Baseline    | 3 months         |     |      |          |                 |     |      |          |                 |
|                  |        | 136.8 ± 7.2 | 122.4 ± 5.1*     | p = 0.02 | p = 0.23 | p = 0.04 |                   |     | 135.9 ± 6.1 | 117.4 ± 6.2* | p = 0.03 | p = 0.31 | p = 0.04 |
| DBP (mmHg)       |        | Baseline    | 3 months         |     |      |          |                 |     |      |          |                 |
|                  |        | 80.3 ± 6.1  | 78.4 ± 3.4*      | p = 0.03 | p = 0.46 | p = 0.02 |                   |     | 79.1 ± 5.1  | 74.4 ± 7.0* | p = 0.04 | p = 0.61 | p = 0.03 |

BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure; WC: waist circumference. Statistical differences, p < 0.05 in each genotype group (*). No statistical differences between genotype groups.
ACYL-COA SYNTHETASE LONG-CHAIN 5 POLYMORPHISM IS ASSOCIATED WITH WEIGHT LOSS AND METABOLIC CHANGES IN RESPONSE TO A PARTIAL MEAL-REPLACEMENT HYPOCALORIC DIET

BMI (-3.1 ± 0.4 kg/m² vs. -3.4 ± 0.5 kg/m²; p = 0.02), fat mass (-5.2 ± 1.4 kg vs. -6.4 ± 1.2 kg; p = 0.01) and waist circumference (-6.1 ± 1.1 cm vs. -8.6 ± 0.8 cm; p = 0.02) than non T allele carriers.

Table III lists biochemical parameters. After the dietary intervention with meal replacement hypocaloric diet, only subjects with a T allele showed a significant improvement in triglycerides (CC vs. CT + TT) (-4.6 ± 2.4 mg/dL vs. -14.4 ± 2.3 mg/dL; p = 0.01). After this dietary intervention, subjects with both genotypes showed a significant improvement in insulin levels (-2.0 ± 0.3 mU/L vs. -4.5 ± 0.5 mU/L; p = 0.01) and HOMA-IR (-0.4 ± 0.2 units vs. -1.3 ± 0.3 units; p = 0.02). These improvements in insulin levels and HOMA-IR were higher in T allele carriers than non-T allele carriers.

DISCUSSION

The main finding of this study was that individuals with the T allele of SNP rs2419621 displayed a significantly greater improvement in body weight, fat mass, waist circumference, insulin levels, and HOMA-IR than those who were not carriers of the T allele after a partial meal replacement hypocaloric diet. T allele carriers showed a significant decrease in triglyceride levels, too.

To explain our results we can use a pathophysiological hypothesis. Because of its location in liver mitochondrial membranes, the increased protein expression in response to food deprivation (6), and deficient change in mRNA expression during adipocyte differentiation (14), the ACSL5 isoform is suggested to provide acyl-CoA bound primarily for beta-oxidation rather than triglyceride synthesis (5). For example, FA oxidation is reduced in the muscle tissue of obese black subjects when compared to obese white subjects, and this fact was related to lower ACSL activity in the mitochondria (15). Thus, a genetic variant modifying FA metabolism in the muscle or liver may importantly influence the rate of weight loss and metabolic changes, and the rs2419621 ACSL5 SNP is associated with positive results after a partial-meal replacement hypocaloric diet. This SNP could act as a cis-acting regulatory variant affecting ACSL5 expression levels, and the effect of the T allele on adiposity and biochemical parameters support that this genetic variant may influence the amount of weight loss by increasing ACSL5 levels and promoting the FA beta-oxidation pathway.
In the literature there are intervention studies that have evaluated this genetic variant. For example, Adamo et al. (7), using a total meal replacement diet of 900 calories per day during a short period of 6 weeks, reported better weight responses in T allele carriers. However, this work did not evaluate any metabolic parameters. Rajkumar et al. (8) showed that obesity and overweight subjects carrying the ACSL5 rs2419621 T allele are more responsive to two different dietary interventions in comparison to non-carriers. The caloric restriction targets for two previous cohorts used by these authors (8) were determined by subtracting 500 to 800 calories from the participants’ daily energy needs without a meal replacement strategy. The dietary prescription in this study (8) was higher than our intervention, and ranged from 1,200 to 1,800 calories per day. The diet’s macronutrient composition was different, too (energy intake: 55% carbohydrates, 30% fat, and 15% proteins). Although the dietary intervention was different, the weight loss target was also surpassed in the carriers of the T allele, similar to our work. Rajkumar et al. (8) did not explore any metabolic parameters. However, an important finding was the finding of a greater decrease in visceral fat in the carriers of the T allele as detected by dual-energy X-ray absorptiometry. This finding agrees with the greater decrease in waist circumference found in our work. In addition, this allows to explain our metabolic findings. Excessive accumulation of visceral fat, characterized as fat packed between the inner organs, is associated with impaired metabolic parameters (16). Specifically, this situation entails a rise in lipolytic activity within visceral adipocytes, with an increased delivery of free fatty acids into the liver, resulting in insulin resistance (17,18). The greater decrease in weight, but especially in visceral fat, seen in patients with the T allele explains the greater improvement found in insulin and HOMA-IR levels, together with a significant decrease in triglycerides.

The strength of our study was in its design as an interventional trial with high adherence to a partial-meal replacement diet of practical relevance to the general population. Limitations included the inclusion in the trial of our obese subjects without established cardiovascular disease. Second, we only analyzed one SNP of the ACSL5 gene, so other genetic variants may be associated with our findings. Third, many uncontrolled factors may influence our results (epigenetics, hormonal status, and level of physical activity). Fourth, the absence of a control group without diet may introduce a bias. Finally, self-reported dietary intake is unreliable and may result in under- or over-reporting biases.

In summary, our data suggest that the genetic variant (rs2419621) of the ACSL5 gene is associated with diet response after a partial-meal replacement intervention, with greater improvements in adiposity and biochemical parameters in subjects with the T allele. Finally, identifying predictors of weight loss response is important for tailored lifestyle interventions (19).

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