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RS2289487 variation in *PERILIPIN* gene is a predictor of weight loss and protection against impaired glucose metabolism after a meal-replacement diet in postmenopausal obese females

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Abstract. – OBJECTIVE: The *PERILIPIN1* (*PLIN1*) gene encodes an adipocyte-associated protein that modulates weight. The objective was to evaluate the role of the *rs2289487* genetic variant of the *PLIN1* gene on weight loss and glucose metabolism secondary to a partial meal replacement (pMR) hypocaloric diet.

PATIENTS AND METHODS: We conducted an interventional study in 111 postmenopausal obese females with body mass index (BMI) > 35 kg/m^2. The subjects received two intakes per day of a normocaloric hyperproteic formula for 12 weeks.

RESULTS: After the pMR diet, body weight, (BMI), fat mass, waist circumference, fasting insulin levels and HOMA-IR decreased in both genotype groups. The improvements in these parameters were higher in C allele carriers than in subjects with TT genotype. The percentage of patients who achieved 7.5% weight loss was higher in the C carriers (57.4% *vs.* 27.6%), (adjusted Odds Ratio 2.14, 95% CI = 1.33-9.40; p = 0.02). The decrease in the percentage of diabetes mellitus or impaired fasting glucose decrease was statistically significant in C allele carriers (30.2% *vs.* 18.9%; p = 0.01) (OR 0.54, 95% CI = 0.22-0.78; p = 0.02).

CONCLUSIONS: The C allele of *rs2289487* predicts the magnitude of weight loss resulting from a pMR diet. These adiposity improvements produce a better improvement in insulin resistance and the percentage of impaired glucose metabolism.

Key Words:
Rs2289487, Partial meal replacement, *PLIN1* gene, Weight loss.

Introduction

Obesity is a multifactorial disease related to environmental factors, but also genetic factors. This entity produces high ratios of the main causes of mortality and morbidity, including cardiovascular events, diabetes mellitus type 2, and malignant tumors. The prevalence of this disease in the world is over 10%, and in Spain it is around 22%[1]. Treating obese subjects with diet is a challenge because responses to dietary intervention vary strongly. The most important of these treatments includes a reduced calorie diet with exercise, with the goal of achieving a weight loss of at least 5-10% in a short-term period[2]. One option for the treatment of obese subjects is the diet of partial meal replacements (pMRs). Heymsfield et al[3] performed a detailed evaluation of this approach with a meta-analysis, in this study, the authors demonstrated that pMRs produced superior weight loss than conventional diets, 7% *vs.* 3% in 3 months compared with traditional energy-restricted food-based diets.

Martinez-Botas et al[4] revealed the first data for the role of genetic predisposition in weight responses to interventions, this study reported that some genes are related to short and long-term weight changes. The focus of our study was on the role of a candidate gene for obesity called *PERILIPIN1* (*PLIN1*), which encodes an adipocyte-associated protein that modulates corporal weight through its regulation of metabolism in adipocyte cells, lipolysis, and fat accumulation[5]. *PLIN1* worsens lipolysis and induces triacylglycerol accumulation by diminishing lipolysis action[6]. One single nucleotide variant (SNV) of *PLIN1* (*rs2289487*) has been related to weight loss success after a multidisciplinary program with cognitive behavioral therapy, nutritional advice, and exercise[7]. Taking into account all the previously mentioned data

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and the potential interest in pMRs diets in clinical practice, it seems interesting to evaluate the relationship of this genetic variant with the potential response of this type of nutritional intervention.

The objective of our study was to evaluate the role of *rs2289487* genetic variant of *PLIN1* gene on weight loss secondary to pMR diet.

Patients and Methods

Study Design

In this study, the effect of a 3 3-month partial meal replacement (pMR) diet on body weight and cardiovascular risk factors was analyzed. This non-randomized trial was conducted at a Public Hospital in Spain from January 2019 to July 2021. We prescribed to these subjects a pMR diet with a normocaloric hyperproteic formula.

We recruited 111 postmenopausal obese women with a consecutive method of sampling in our health area. The following inclusion criteria were met for all subjects; menopause, defined as a period of 9-12 months with amenorrhea without pregnancy and follicle-stimulating hormone above 30 UI/L and body mass index (BMI) greater than 35 kg/m^2. Postmenopausal obese women with uncontrolled thyroid disease, previous cardiovascular events (heart attack or stroke), severe renal or hepatic dysfunction, active alcoholism, malignant tumor, active medications known to influence lipid or glucose levels, and multivitamins supplements were excluded.

The next anthropometric data were collected at initial and post-treatment; (corporal weight, height, body mass index (BMI), waist circumference, and fat mass by electrical impedance), and systolic/diastolic blood pressure was measured, too. At the basal time and after 3 months of dietary intervention, fasting blood samples were collected into tubes containing EDTA, for analysis of basal fasting (8 hrs.) glucose, c-reactive protein (CRP), insulin, insulin resistance calculated (HOMA-IR), total cholesterol, LDL-cholesterol, HDL-cholesterol, and plasma triglycerides. In order to diagnose the presence of diabetes mellitus or impaired fasting blood glucose, the criteria were glucose > 126 mg/dl or > 110 mg/dl respectively[8]. The variant of *PLIN1* gene was assessed by real-time polymerase chain reaction (PCR).

Program Description

The postmenopausal obese females included in the study received nutritional instructions to complete a meal-replacement hypocaloric diet (pMR). This pMR was distributed in 6 meals: breakfast, morning snack, lunch, afternoon snack, dinner, and dinner snack. The next two meals (lunch and dinner) were substituted by a normocaloric hyperproteic formula (VEGESTART Complete®), whose composition is reported in Table I, and the remaining intakes were completed with foods. A dietitian gave reinforcement by phone call twice per week and all subjects reported their dietary intakes of 72 hours in order to estimate the daily intakes of calories and macronutrients, before and after 3 months of dietary intervention. The dietary registrations were evaluated with professional software (Dietsource®, Nestlé, Geneve, Switzerland). The allowed physical activity for subjects was the following: aerobic physical activities at least 3 times per week (60 minutes each) and the proposed exercises were walking, running, cycling, and swimming. Physical activity was self-reported through a questionnaire by each subject.

Adiposity Parameters and Arterial Blood Pressure

The data collected at enrolment and after 3 months were obtained according to standardized techniques. The height was estimated with the patient in an upright using a stadiometer (Omrom, Los Angeles, CA, USA). The corporal weight was measured without clothing with an accuracy of 10

Table I. Distribution of calories and macronutrients in the partial Meal replacement diet (four intakes as natural food and two intakes as artificial formula).

DATA	Oral diet + intake	Normocaloric hyperproteic formula (200 ml per brick)
Calories (kcal)	1,035	200
Proteins [g (%TCV)]	64.4 (25%)	15.4 (31%)
Fats [g (%TCV)]	19.1 (17%)	5.2 (23%)
Carbohydrates [g (%TCV)]	151.6 (59%)	21 (42%)
Dietary Fiber (g)	15.9	4.2

Normocaloric hyperproteic formula is VEGESTART® (%TCV: % Total Caloric Value).

gr, using a manual scale. The BMI was calculated using the above-mentioned parameters with the following equation: Weight (kg) / Height x Height (m^2). The difference in relative weight was determined by the percentage of weight loss (%PP) with the formula [Weight before intervention - Weight after intervention (kg) / Initial weight (kg)] x 100. A loss of more than 7.5% of the initial weight was considered a success.

A bioelectrical impedance analysis (BIA) was conducted. An alternating current of 0.8mA at 50 kHz was produced by a calibrated signal generator (EFG, Akern, Florence, Italy). The equation of this device was used (0.756 Height^2/Resistance) + (0.110 x Body mass) + (0.107 x Reactance) – 5.463. The parameters analyzed with the BIA were total fat mass (kg)[9]. Finally, waist circumference was determined with the patient standing in the narrowest diameter between xiphoid process and the iliac crest using an extendable tape measure (Omrom, Los Angeles, CA, USA). A bioelectrical impedance analysis (BIA) was also conducted.

In each subject and in both times, arterial blood pressure was determined three times after a 10-minute rest with a random zero mercury sphygmomanometer and averaged.

Biochemical Parameters

Biochemical measurements, including glucose, insulin, C reactive protein CRP), total cholesterol, HDL-cholesterol, and triglyceride levels using the COBAS INTEGRA 400 analyzer (Roche Diagnostic, Basel, Switzerland). LDL cholesterol was determined using Friedewald formula (LDL cholesterol = total cholesterol-HDL cholesterol-triglycerides/5)[10]. Based on these parameters, homeostasis model assessment for insulin resistance (HOMA-IR) was calculated using these values (glucose x insulin/22.5)[11].

The genomic DNA was obtained using a commercial kit as indicated by manufactured (Applied Biosystems, Foster City, CA, USA) from oral mucosa cells. Genotyping (RS2289487) was performed by using commercial assays with the TaqMan® OpenArray™ Genotyping platform (Thermofisher, Pittsburg, PA, USA). Samples of DNA were loaded using the AccuFill system, and amplification was conducted on the QuantStudio 12K Flex Real-Time qPCR instrument (Thermofisher, Pittsburg, PA, USA). A volume of 25 µl with 2.5 µl TaqMan Open Array Master Mix (Applied Biosystems, Foster City, CA, USA) and 2.5 µl human DNA sample were used and amplified on arrays following the manufacturer's instructions. During the polymerase chain reaction, DNA was denaturated at 95ºC for 3 min; this was followed by 45 cycles at 95ºC for 15 s and annealing at 59.3ºC for 45 s, with an extension step of 60ºC for 5 min with hot start Taq DNA polymerase. Genotype calling and sample clustering for OpenArray assays were performed in TaqMan Genotyper (LifeTechnologies, Carlsbad, CA, USA).

Statistical Analysis

Statistical analysis was conducted with SPSS version 23.0 (IBM Corp., Armonk, NY, USA). The genotype distribution was studied for deviation from Hardy-Weinberg equilibrium by a Chi-square. Sample size was calculated to detect differences over 3 kg with 90% power and 5% significance (n = 110). All parameters were examined for normality with the Kolmogorov-Smirnov test. The results were reported as average+/- standard deviation. In within-groups, we used paired Student *t*-test for biochemical parameters at baseline and after 3 weeks of pMR. In between groups, an independent *t*-test was utilized to compare the differences. The Mann-Whitney U test was utilized in non-parametric variables. Categorical variables were evaluated with the Chi-Square test, with Yates correction as necessary. The statistical analysis to evaluate the gene-diet interaction was a univariate analysis of covariance (ANCOVA) with the Bonferroni test post-hoc. The statistical analysis was conducted for the combined genotypes CC and TC as a group and TT genotype as a second group (wild type genotype), with a dominant model. Logistic regression analyses were used to the calculated odds ratio (OR) and 95% confidence interval (CI) to estimate the association of the *rs2289487* variant with weight loss as dichotomic (7.5% weight loss) and presence of alteration of glycemic metabolism (diabetes mellitus or impaired fasting glucose). A p-value < 0.05 was considered significant.

Results

We recruited 111 postmenopausal obese females with the following distribution of genotypes [38 TT (34.2%), 63 TC (56.8%) and 10 CC (9.0%)]. The variant of *PLIN1* gene was in Hardy Weinberg equilibrium (p = 0.42). All obese subjects completed the 3-month follow-up period without dropouts. Finally, no adverse events secondary to the dietary intervention were observed. The average age of all subjects was

60.8 ± 3.9 years (range: 49-62 years), and the average age was similar in both genotype groups [wild type (TT) *vs.* mutant type (TC+CC)] (60.1 ± 3.1 years *vs.* 61.3 ± 4.0 years: ns).

In this interventional study, obese subjects with both genotypes (TT *vs.* TC+CC) showed a decrease in daily intake of energy, carbohydrate, fat, and protein. These changes (Table II) were statistically significant in the above-mentioned parameters, only dietary fiber remained unchanged. The final distribution of type of fats in both genotype groups was similar (TT *vs.* TC+CC); 32.3% *vs.* 33.5% of saturated fats, 50.3% *vs.* 49.6% of monounsaturated fats and 17.4% *vs.* 18.1% of polyunsaturated fats. In subjects with TT genotype, 90% of all the prescribed VEGESTAR® bricks were taken, and in subjects with the TC+CC genotype, 92%. Physical activity in subjects with TT genotype was similar in both times (baseline and 3 months) (119.2 ± 22.3 min/week *vs.* 130.1 ± 28.2 min/week: $p = 0.71$). Finally, C allele carriers maintained the same physical activity (113.3 ± 32.9 min/week *vs.* 128.8 ± 30.2 min/week: $p = 0.45$).

As shown in Table III, the arterial pressure levels were similar in both genotypes at baseline. Moreover, adiposity parameters were higher in subjects with TT genotype than C allele carriers, these statistical differences were detected at basal time and after 3 months of intervention. After the partial-meal replacement hypocaloric diet, body weight, body mass index (BMI), fat mass, waist circumference, systolic pressure and diastolic pressure decreased in both genotype groups. The improvements in these parameters were higher in C allele carriers than in subjects with TT genotype. The percentage of subjects who achieved 7.5% weight loss was higher in the C carriers (57.4% *vs.* 27.6%), with a different average of weight loss (-9.5 ± 0.3 kg *vs.* -6.2 ± 0.5 kg:

Table II. Average daily intakes and physical activity at basal time and after 3 months of intervention (mean ± SD).

	N = 111						
	TT (n = 38)			TC+CC (n = 73)			
Daily intakes	Basal	3 months	*p* Time	Basal	3 months	*p* time	*p* Time Genotype Basal Genotype Post treatment Genotype
Calorie intake (kcal/day)	1,628.9 ± 11.8	1,017.9 ± 29.1*	$p = 0.01$	1,641.1 ± 181.2	1,011.4 ± 32.1*	$p = 0.02$	$p = 0.32$ $p = 0.43$ $p = 0.53$
Carbohydrate intake (g/day) (PTC%)	169.8 ± 51.9 (39.4%)	131.8 ± 21.1$ (63.4%)	$p = 0.02$	168 ± 43.1 (39.1%)	130.1 ± 39.1$ (63.2%)	$p = 0.02$	$p = 0.41$ $p = 0.58$ $p = 0.42$
Fat intake (g/day) (PTC%)	58.8 ± 20.3 (37.1%)	26.1 ± 12.1# (22.6%)	$p = 0.01$	59.2 ± 18.3 (37.3%)	27.1 ± 8.3# (22.7%)	$p = 0.01$	$p = 0.49$ $p = 0.36$ $p = 0.41$
Protein intake (g/day) (PTC%)	74.1 ± 14.1 (23.5%)	54.1 ± 12.3& (23.0%)	$p = 0.02$	74.9 ± 13.1 (23.6%)	56.2 ± 12.9& (23.3%)	$p = 0.03$	$p = 0.44$ $p = 0.51$ $p = 0.23$
Fiber intake (g/day)	16.2 ± 6.0	17.3 ± 4.9	$p = 0.23$	15.8 ± 5.2	16.9 ± 4.2	$p = 0.42$	$p = 0.21$ $p = 0.52$ $p = 0.18$
Physical activity (min/week)	120.2 ± 12.0	127.3 ± 12.9	$p = 0.22$	125.8 ± 9.2	131.9 ± 13.2	$p = 0.41$	$p = 0.29$ $p = 0.42$ $p = 0.38$

PTC: Percentage of total calorie; Statistical differences $p < 0.05$, in each genotype group (*Daily Calorie intake, $Daily Carbohydrate intake, #Daily fat intake, &Daily protein intake). Last column: No statistical differences between basal values, post-treatment values, and changes between both genotype groups.

Table III. Adiposity parameters and arterial pressure (mean ± SD).

	N = 111						
	TT (n = 38)			TC+CC (n = 73)			
Parameteres	Basal	3 months	*p* Time	Basal	3 months	*p* time	*p* Time Genotype Basal Genotype Post treatment Genotype
BMI	40.2 ± 2.3	38.6 ± 2.0*	$p = 0.03$	39.4 ± 2.0	36.2 ± 2.1*	$p = 0.02$	$p = 0.02$ $p = 0.03$ $p = 0.02$
Weight (kg)	100.6 ± 6.5	94.4 ± 5.1$	$p = 0.02$	97.1 ± 3.1	87.6 ± 4.1$	$p = 0.01$	$p = 0.02$ $p = 0.03$ $p = 0.03$
Fat mass (kg)	49.4 ± 4.1	45.5 ± 6.1#	$p = 0.03$	48.1 ± 3.0	40.4 ± 3.1#	$p = 0.01$	$p = 0.03$ $p = 0.02$ $p = 0.01$
WC (cm)	120.2 ± 4.1	113.1 ± 4.0&	$p = 0.01$	117.1 ± 3.9	109.0 ± 2.1&	$p = 0.001$	$p = 0.01$ $p = 0.02$ $p = 0.03$
SBP (mmHg)	131.4 ± 4.0	124.9 ± 5.1**	$p = 0.02$	132.8 ± 6.1	124.9 ± 5.0**	$p = 0.02$	$p = 0.13$ $p = 0.28$ $p = 0.21$
DBP (mmHg)	83.5 ± 5.0	77.2 ± 3.1***	$p = 0.03$	81.3 ± 4.0	76.2 ± 5.0***	$p = 0.03$	$p = 0.24$ $p = 0.31$ $p = 0.23$

BMI: body mass index DBP, diastolic blood pressure; SBP, systolic blood pressure; WC, waist circumference; Statistical differences $p < 0.05$, in each genotype group (*BMI, $Weight, #fat mass, &WC, **SBP, ***DBP). Last column: Statistical differences between basal values, post-treatment values and changes between both genotype groups (BMI, weight, fat mass and WC).

$p = 0.02$). The odds ratio to achieve 7.5% weight loss adjusted by age and initial weight was (OR = 2.14, 95% CI = 1.33-9.40; $p = 0.02$)

Table IV illustrates all biochemical parameters. Total cholesterol, LDL- cholesterol, fasting insulin levels and HOMA-IR improved in both genotype groups. Moreover, after dietary intervention with the meal replacement hypocaloric diet, the improvement in insulin resistance as HOMA-IR and insulin levels were higher in C allele carriers. In the TT genotype group, the presence of diabetes mellitus or impaired fasting glucose did not show statistical differences (27.6% *vs.* 24.1%; $p = 0.11$). Moreover, the decrease in the percentage of patients with altered fasting glucose levels was statistically significant in C allele carriers (30.2% *vs.* 18.9%; $p = 0.01$). The odds ratio to improve alteration in glucose metabolism adjusted by age and weight loss was (OR = 0.54, 95% CI = 0.22-0.78; $p = 0.02$). It would be necessary to treat (number needed to treat), a total of 8.83 subjects with the C allele for the disappearance of a case of diabetes mellitus or impaired blood glucose in the fasting state NNT 8.83 (95% CI: 3.6-20.2; $p = 0.03$).

Discussion

Our observations on the genetic variant of the *PLIN1* gene reaffirm some previous findings, C allele carriers of SNV *rs2289487* showed a significantly greater improvement in weight loss, insulin resistance and percentage of subjects with impaired fasting glucose/diabetes mellitus after a partial meal replacement (pMR) hypocaloric diet. Postmenopausal obese females with the C allele showed lower pre- and post-intervention adiposity parameters and insulin resistance than non-C allele carriers.

The PERILIPINS are part of a family of proteins that interact with the surfaces of intracellular lipid droplets. These proteins have been called the PAT family, after the initial member PERILIPIN and two other members, ADRP and TIP-47[12]. The most important protein of this family expressed in adipose tissue[13] regulates fat storage, by modulating hormone-sensitive lipase, which produces hydrolysis of triacylglycerol. *In vivo* studies[14] have reported that the loss of the *PLIN* gene produces a lean phenotype and protects against a high-fat diet. In human studies15, a gender interaction with the genetic variant *rs2289487* at position 6209

Table IV. Biochemical parameters in both genotype groups (mean±SD). HOMA-IR (Homeostasis model assessment).

	N = 111						
	TT (n = 38)			TC+CC (n = 73)			
Biochemical Parameteres	Basal	3 months	*p* Time	Basal	3 months	*p* time	*p* Time Genotype Basal Genotype Post treatment Genotype
Glucose (mg/dl)	101.3 ± 4.1	97.6 ± 3.1	*p* = 0.23	103.1 ± 3.1	96.8 ± 4.2	*p* = 0.08	*p* = 0.12 *p* = 0.51 *p* = 0.21
Total cholesterol (mg/dl)	215.1 ± 9.7	192.1 ± 8.2*	*p* = 0.01	213.9 ± 5.8	190.8 ± 7.2	*p* = 0.01	*p* = 0.43 *p* = 0.52 *p* = 0.19
LDL-cholesterol (mg/dl)	136.2 ± 5.3	115.1 ± 4.1 $	*p* = 0.02	134.9 ± 4.1	114.2 ± 3.9	*p* = 0.03	*p* = 0.61 *p* = 0.80 *p* = 0.39
HDL-cholesterol (mg/dl)	56.2 ± 3.1	54.9 ± 3.2 #	*p* = 0.45	56.2 ± 4.1	54.8 ± 3.4	*p* = 0.53	*p* = 0.32 *p* = 0.61 *p* = 0.39
Triglycerides (mg/dl)	115.4 ± 10.1	100.2 ± 8.2##	*p* = 0.01	112.1 ± 13.2	99.8 ± 10.1	*p* = 0.03	*p* = 0.11 *p* = 0.23 *p* = 0.14
Insulin (mUI/l)	15.4 ± 0.9	12.6 ± 1.1&	*p* = 0.03	16.1 ± 1.1	9.9 ± 1.9&	*p* = 0.01	*p* = 0.02 *p* = 0.12 *p* = 0.03
HOMA-IR	4.5 ± 0.3	3.3 ± 0.4**	*p* = 0.03	4.7 ± 0.2	2.8 ± 0.3**	*p* = 0.01	*p* = 0.01 *p* = 0.33 *p* = 0.02

Statistical differences $p < 0.05$, in each genotype group (*Total cholesterol, $LDL-Cholesterol, #HDL-cholesterol, ## Triglycerides, &insulin, **HOMA IR). Last column: Statistical differences in post-treatment values and changes between both genotype groups (insulin and HOMA-IR).

(*PLIN* T>C) of the *PLIN* gene was reported in females, but not in males. In this investigation, the C allele was associated with low body mass index and corporal weight, and it generated a reduced risk of obesity[15]. In other studies[16], the presence of the C allele was related to a lower postprandial response that induced a lower atherogenic risk.

Some nutritional intervention studies[17] have evaluated the role of this genetic variant in the weight response. For example, Soenen et al[17] reported that the minor C allele of *rs2289487* produced larger body weight loss and fat loss over time in females with a very low-calorie diet for six months. This diet consisted of 500 cal/day, and it provided 52 g of protein, 7 g of fat, and 50 g of carbohydrates. This dietary intervention presented a greater protein caloric restriction than the diet that we have used in our current study, and the intervention has a shorter duration. Moreover, the influence of this genetic variant on the body weight response in females was similar; therefore, we deduce that this response does not depend on the type of diet or distribution of nutrients, but rather on the caloric restriction, that produces secondary weight loss. In addition, the association with waist circumference is of particular interest in both studies, since this implies that it is especially related to visceral obesity, one of the metabolic syndrome factors[18].

In another interventional study, Aller et al[7] reported a high weight loss in the first 3 months and a trend for higher weight loss over 12 months after an intensive lifestyle multidisciplinary program (physical activity program, cognitive behavioral therapy, and nutritional advice without an individual target in energy restriction) in females. The sample of patients in this study from the point of view of BMI is very similar to ours. Moreover, in the study by Soenen et al[17], the mean BMI was 30 kg/m^2, and they reported the same difference in weight loss in C allele carriers. On the other hand, in previous studies[18,19], this genetic variant predicted the percentage of subjects with a loss greater than 5%18, in our study, it even predicted

losses greater than 7.5%. Similarly, Garaulet et al[19] reported in the ONTIME study (Obesity, Nutrigenetics, Timing, Mediterranean) that the probability of being a higher responder (percentage of weight loss above 7.5%) after a Mediterranean diet for 6 months was higher among C carriers. Although the physiological mechanism for these associations has not been elucidated, we hypothesize, on the basis of previous literature, that C carriers at *rs2289487* variant have a lower concentration of *PLIN1* in visceral adipose tissue and higher lipolysis activity[20], producing an increased fat mobilization under the specific parameters of dietary intervention. It has been reported that the transcription of PERILIPIN may differ in visceral adipose tissue from adipose tissue in other locations and central obesity may affect the expression of PERILIPIN[21,22].

Regarding the association of different SNP with the risk of diabetes mellitus, Qi et al[15] have reported that central obesity may change the association of this *PLIN* genetic variation with diabetes risk in a sample of females with obesity. Our study validates this previous finding in an interventional study showing how C allele carriers improve the prevalence of diabetes mellitus and impaired fasting blood glucose after a higher amount of weight loss.

Limitations

Our study has some limitations. First, the inclusion in the trial of our postmenopausal obese females with low cardiovascular risk does not allow the generalization of the results beyond a population of obese without comorbidities. Second, we only analyzed one SNP of *PLIN* gene, so other variants could be associated with our findings. Third, many other uncontrolled factors could influence our results (epigenetic, hormonal status, and timing of food, for example). Fourth, the absence of a PERILIPIN determination might be a bias. Fifth, the lack of determination of HbA1c and other biochemicals could be a problem. Finally, the self-reported dietary intake might include bias of under- or over-reporting energy.

Conclusions

In conclusion, C allele of *rs2289487* predicts the magnitude of weight loss resulting from a pMR diet. We reported that C allele carriers lost more weight, fat mass and waist circumference. These adiposity improvements produce a better response to insulin resistance and decrease the percentage of impaired glucose metabolism. Therefore, our results must be investigated in other groups and with other distributions of macronutrients and restrictions of energy intake. Results may have practical implications in personalized nutrition based on genotyping prior to dietary treatment of obese subjects with this genetic variant, which could help predict the weight response and decrease in the presence of glycemic alteration.

Ethics Approval

This study protocol was reviewed and approved by the HCVUA Committee, approval number (HVUVA committee 2/2018).

Informed Consent

Written Informed consent was obtained from all individual participants included in the study.

Conflict of Interest

The authors have no conflicts of interest to declare.

Funding

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Authors' Contributions

Daniel Antonio de Luis designed the study and wrote the article.
Olatz Izaola and Rocio Aller realized nutritional evaluation.
David Primo and Daniel de Luis realized biochemical evaluation.

Data Availability

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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