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# FTO variant RS 1121980 interact with metabolic response after weight loss with a meal replacement hypocaloric diet in Caucasian obese subjects

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**Abstract. – OBJECTIVE: One genetic variant (rs1121980) of FTO gene has been related with body mass index and visceral adiposity. The objective of our study was to investigate the role of rs1121980 genetic variant of FTO gene on weight loss and metabolic changes secondary to a partial meal replacement (pMR) hypocaloric diet.**

**PATIENTS AND METHODS: We conducted an interventional study on 219 obese Caucasian subjects with body mass index (BMI) > 30 kg/m². The subjects received two intakes per day of a normocaloric hyperproteic formula for 12 weeks. Adiposity and biochemical parameters (lipid profile, insulin, homeostasis model assessment (HOMA-IR) and glucose) were determined.**

**RESULTS: After the pMR diet, body weight, BMI, fat mass, waist circumference, blood pressure, total-cholesterol, LDL-cholesterol, triglyceride, fasting insulin levels and HOMA-IR decreased in both genotype groups. The improvements in adiposity parameters and some biochemical parameters (insulin, HOMA-IR, triglyceride levels) were bigger in non-T allele carriers than in T allele carriers. The percentage of patients who achieved 7.5% weight loss was higher in the non-T carriers (76.7% *vs.* 48.4%), also with a different average of weight loss (-12.3±0.3 kg *vs.* -5.9±0.5 kg: *p*=0.01). The odds ratio to achieve 7.5% of weight loss was (OR= 2.22, 95% CI=1.24-4.01; *p*=0.02).**

**CONCLUSIONS: Non-T allele carriers of rs1121980 show a higher magnitude of weight loss and improvement in adiposity parameters, insulin, HOMA-IR and triglyceride levels resulting from a pMR diet than T allele carriers.**

*Key Words:*
Rs1121980, Partial meal replacement diet, FTO gene, Weight loss.

## Introduction

Obesity is a serious risk factor for non-communicable diseases, and it is the fifth leading cause of death in the world[1]. This entity generates high ratios of morbidity including cardiovascular events, diabetes mellitus type 2 and malignant tumours. The prevalence of obesity is dramatically increasing, emphasising the emergency in development of strategies for obesity treatment and prevention[2].

Therefore, understanding the interactions between nutritional factors and genetic background could be helpful in developing strategies for an accurate treatment of obesity. The most common method used in the treatment of obesity is a low-calorie diet with exercise, with the goal of achieving a weight loss of at least 5-10% in a short-term period[3]. One option among low-calorie diets is the diets of partial meal replacements (pMRs). Recently, a meta-analysis has demonstrated that pMRs produced superior weight loss than conventional diets, 7% *vs.* 3% in 3 months comparing with traditional energy restricted food-based diets[4].

In this context, single nucleotide polymorphism (SNP) of the fat mass and obesity associated (FTO) gene, as the strongest genetic determinant of obese. These genetic variants increase appetite and consequently increase the risk of obesity[5,6]. Specifically, one genetic variant (rs1121980) of FTO gene has been related with body mass index and visceral adiposity[7]. The exact way of FTO gene could affect body mass index (BMI) and adiposity parameters is not clear, possibly it is related with a role in determination of energy expenditure or energy intake. Interactions between this polymorphism of the FTO gene (rs1121980) and dietary interventions have only been examined in few studies, none of which specifically examined the effect of a hypocaloric diet and neither the effect of a pMR diet[7-11]. Some



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of the studies are based on cross-sectional data and they have evaluated relationship between lifestyle influences and the rs1121980 on body weight changes[8,11]. Other studies[7,9,10,11] have evaluated the interactions of different dietary patterns, dietary diversity, Mediterranean diet, and dietary fat intake with the effect on BMI of this SNP.

Considering all the previously mentioned data and the potential interest in pMRs diets in clinical practice, it seems interesting to study the relationship of rs1121980 with the potential response of this dietary intervention. The objective of our study was to investigate the role of rs1121980 genetic variant of FTO gene on weight loss and metabolic changes secondaries to a pMR hypocaloric diet.

## Patients and Methods

### Study Design

This non-randomized trial of one arm was conducted at a Tertiary Hospital from January 2020 to December 2022. In this study, we prescribed to obese subjects a pMR diet with a normocaloric hyperproteic formula during 12 weeks.

We enrolled 219 Caucasian obese subjects with a consecutive method of sampling in our Health Area. All subjects agreed to participate in the investigation, and all these patients gave an informed consent. The study was realized in accordance with the Declaration of Helsinki and the Ethics Committee approved the protocol (code of registration 07/2020). The inclusion criterion for this study were the following: obesity assessed as body mass index $\geq$ 30 kg/m$^2$ and an age range of 20-65 years. Obese subjects with one or more of the following data were excluded from the study: a severe illness (e.g., chronic kidney disease, chronic liver disease, heart failure, previous cardiovascular events, and malignant tumours) and history of alcoholism. Following a hypocaloric diet in the previous 6 months or active treatments with statins, fibrates, and drugs against diabetes mellitus that modify insulin resistance were also exclusion criteria.

The next anthropometric parameters were recorded pre- and post-treatment; (corporal weight, height, body mass index (BMI), waist circumference and fat mass by electrical bioimpedance). Blood pressure was also measured. In both times fasting blood samples were collected into ethylenediaminetetraacetic acid EDTA-coated tubes, for analysis of basal fasting (8 hs) glucose, insulin, insulin resistance estimated by Homeostasis model assessment (HOMA-IR), total cholesterol, LDL-cholesterol, HDL-cholesterol and plasma triglycerides. All biochemical parameters were measured at initial and post-treatment. The variant of FTO gene was assessed by real-time polymerase chain reaction.

### Program Description

After signing the informed consent, the obese subjects received nutritional instructions to follow the completion of a meal-replacement hypocaloric diet (pMR). This pMR diet was distributed in 6 meals: breakfast, morning snack, lunch, afternoon snack, dinner, after dinner snack. The lunch and dinner meals were substituted by a normocaloric hyperproteic formula (VEGESTART Complete®, Pueblonuevo del Guadiana, Spain). The composition of this oral formula is shown in Table I. A dietitian gave reinforcement by phone call twice per week. At basal time and after 12 weeks, all patients reported their dietary intakes of 72 hours in order to estimate the calories and macronutrients intakes. The macronutrients and calorie intakes were evaluated with a nutritional software (Dietsource®, Nestlé, Geneve, Switzerland). The allowed physical activity for patients was the following: aerobic physical

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

| | Oral diet + formula | Normocaloric hyperproteic formula (200 ml per brick) |
|---|---|---|
| Calories (kcal) | 1035 | 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).

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 with a questionnaire by each subject.

### Adiposity Parameters and Arterial Blood Pressure

The data collected at enrolment and after 12 weeks were obtained according to standardized techniques. Waist circumference was measured with a flexible standard tape (Omrom Corp., Lake Forest, IL, USA) positioned between the upper border of the iliac crest and the last rib. Two non-consecutive measurements were made, and the average was considered as the final measurement. Body height (cm) was measured using a standard height measurement scale (Omrom Corp., Lake Forest, IL, USA). Body weight was measured while the subjects were minimally unclothed and not wearing shoes, using digital scales (Omrom Corp., Lake Forest, IL, USA). Body mass index (BMI) was obtained with the next equation; weight in kilograms divided by height in squared meters. The difference in relative weight was determined by the percentage of weight loss (%PP) with the next 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. Total fat mass was obtained by impedance with an accuracy of 5 g (EFG BIA 101 Anniversary, Akern, Pontassieve, Italy)[12]. An alternating current of 0.8 mA at 50 kHz produced by a calibrated signal generator (EFG, Akern, Pontassieve, Italy) The equation of this device was used (0.756 Height$^2$/Resistance) + (0.110xBody mass) + (0.107xReactance) – 5.463.

Blood pressures were obtained with a sphygmomanometer (Omrom, Lake Forest, IL, USA), after the subjects sat for 10 minutes during the interview with four repetitions per patient. The first measurement was discarded and the mean of these three determinations was used

### Parameters

Biochemical measurements, including glucose, insulin, total cholesterol, HDL-cholesterol, and triglyceride levels using the COBAS INTEGRA 400 analyser (Roche Diagnostic, Basel, Switzerland). LDL cholesterol was determined using Friedewald formula (LDL cholesterol=total cholesterol-HDL cholesterol-triglycerides/5)[13]. Based on these parameters, homeostasis model assessment for insulin resistance (HOMA-IR) was calculated using these values (glucose x insulin/22.5)[14].

The genomic DNA was obtained using a commercial kit as indicated by manufactured (Applied Biosystems, Foster City, CA, USA) from oral mucosa cells. Genotyping (rs1121980) was realized by using commercial assays with the TaqMan® OpenArray™ Genotyping platform (Thermo Fisher, Waltham, MA, USA). Samples of DNA were loaded using the AccuFill system. In the next step, amplification was realized on the QuantStudio 12K Flex Real-Time qPCR instrument (Thermo Fisher, Waltham, MA, USA). A volume of 25 µl with 2.5 µl TaqMan Open Array Master Mix (Applied Biosystems, Waltham, MA, USA) and 2.5 µl human DNA sample were used and amplified on arrays following the manufacturer's instructions, too. During the polymerase chain reaction, DNA was denaturated at 90ºC for 4 min; this was followed by 50 cycles at 97ºC for 10 s and annealing at 60.1º C for 50 s, with an extension step of 60ºC for 7 min with hot start Taq DNA polymerase. Genotype calling and sample clustering for OpenArray assays was performed in TaqMan Genotyper (LifeTechnologies, Carlsbad, CA, USA).

### Statistical Analysis

Statistical analysis was realized with SPSS version 23.0 (SPSS 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 2.5 kg with 90% power and 5 % significance (n=210). The normality of the variables was tested using the Kolmogorov-Smirnov test. In order to describe the protocol parameters, measures of central tendency (median) and dispersion measures (standard deviation) were used for continuous variables. Percentage and absolute values were used for categorical parameters. Pearson's Chi-square test was used to compare categorical parameters. Variables were analyzed with student's *t*-test (for normally distributed variable) or Mann-Whitney U test (for non-normally distributed variable). The statistical analysis to evaluate the gene-diet interaction was a univariate analysis of covariance (ANCOVA) with Bonferroni test post-hoc. The statistical analysis was realized for the combined genotypes CT and TT (mutant genotype) as a group and CC

genotype as second group (wild type genotype), with a dominant model. A $p$-value < 0.05 was considered significant.

## Results

We enrolled 219 Caucasian obese subjects with the following distribution of genotypes [56 CC (25.6%), 111 CT (50.7%) and 52 TT (23.7%)]. The variant of FTO gene was in Hardy Weinberg equilibrium ($p$=0.31). All obese subjects completed the 12 weeks follow-up period without drop-outs (Figure 1). No adverse events were reported during the pMR diet.

The average age was 61.8±3.1 years (range: 48-63 years), the average age was similar in both genotype groups [wild type (CC) *vs.* mutant type (CT+TT)] (61.9±3.2 years *vs.* 61.2±4.0 years: $p$=0.56). Sex distribution was similar in both genotypes, [wild type (CC) *vs.* mutant type (CT+TT)] (21.4% males *vs.* 78.6 % females) *vs.* (30.1% males *vs.* 69.9 % females) $p$=0.63.

In this single-arm intervention study, obese subjects with both genotype groups (CC *vs.* CT+TT) showed a decrease in calories, carbohydrate, fat, and protein intakes. These modifications (Table II) were statistically significant in all the above-mentioned parameters. Dietary fibre intake remained unchanged. After 12 weeks of dietary intervention, the distribution of type of dietary fats in both genotype groups was similar (CC *vs.* CT+TT); 32.0% *vs.* 33.2% of saturated fats, a 50.5 % *vs.* 49.8 % of monounsaturated fats and a 17.5 % *vs.* 18.2 % of polyunsaturated fats.

Regarding the completion of the intake of the normocaloric hyperproteic formula (VEGE-

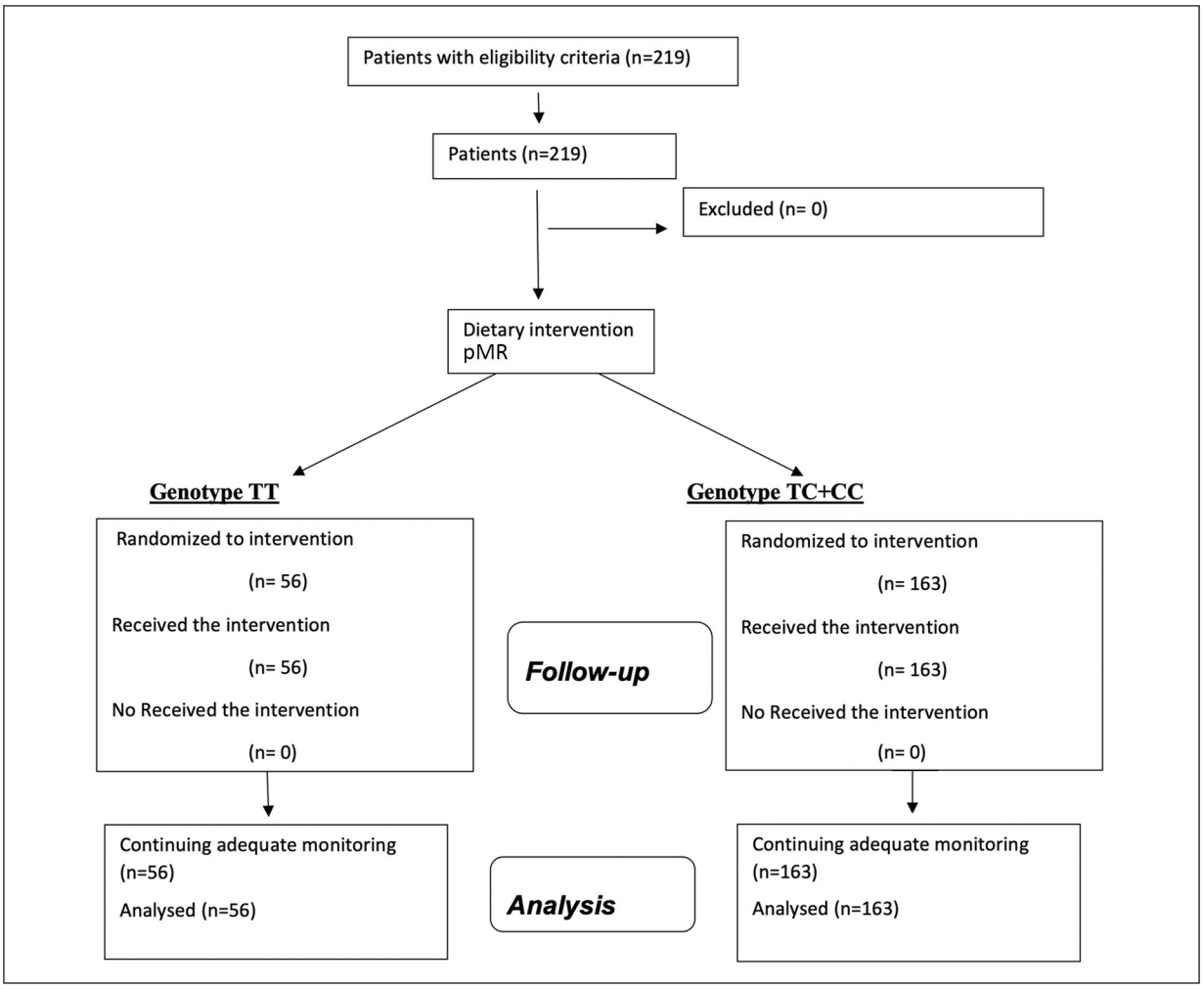


**Figure 1.** Flow chart of patients.

**Table II.** Average daily intakes and physical activity at basal time and after 12 weeks of intervention (mean ± SD).

| Parameteres | N = 219 | | | | | | *p* deltas between genotype changes *p* basal genotype *p* post treatment genotype |
|---|---|---|---|---|---|---|---|
| | CC (n = 56) | | | CT+TT (n = 163) | | | |
| | Basal | 12 weeks | *p*-time | Basal | 12 weeks | *p*-time | |
| Calorie intake (kcal/day) | 1693.9 ± 221.2 | 1033.1 ± 1 8.1* | $p = 0.01$ | 1695.2 ± 132.1 | 1028.1 ± 31.1* | $p = 0.02$ | $p = 0.31$<br>$p = 0.49$<br>$p = 0.52$ |
| Carbohydrate intake (g/day) (PTC%) | 172.8 ± 31.1 (40.1%) | 132.5 ± 20.1$^{\$}$ (63.2%) | $p = 0.02$ | 168.1 ± 23.0 (39.9%) | 130.9 ± 31.0$^{\$}$ (63.2%) | $p = 0.02$ | $p = 0.49$<br>$p = 0.58$<br>$p = 0.47$ |
| Fat intake (g/day) (PTC%) | 58.2 ± 12.3 (36.5%) | 26.2 ± 10.9$^{\#}$ (22.7%) | $p = 0.01$ | 57.2 ± 11.3 (36.7%) | 27.0 ± 8.0$^{\#}$ (22.7%) | $p = 0.02$ | $p = 0.46$<br>$p = 0.33$<br>$p = 0.42$ |
| Protein intake (g/day) (PTC%) | 72.2 ± 13.1 (23.4%) | 54.0±12.0$^{\&}$ (23.1%) | $p = 0.02$ | 72.9 ± 12.1 (23.4%) | 56.2 ± 12.9$^{\&}$ (23.3%) | $p = 0.03$ | $p = 0.45$<br>$p = 0.50$<br>$p = 0.21$ |
| Fiber intake (g/day) | 16.8 ± 6.1 | 17.1 ± 4.1 | $p = 0.28$ | 15.9 ± 5.0 | 16.2 ± 4.0 | $p = 0.43$ | $p = 0.29$<br>$p = 0.57$<br>$p = 0.18$ |
| Physical activity (min/week) | 122.1 ± 11.2 | 125.3 ± 9.9 | $p = 0.26$ | 123.8 ± 7.2 | 130.1 ± 10.2 | $p = 0.30$ | $p = 0.26$<br>$p = 0.41$<br>$p = 0.39$ |

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 deltas between both genotype groups.

START Complete®, Incheon, South Korea), subjects with CC genotype took 93% of all the prescribed bricks and 95% in obese subjects with the CT+TT genotype. Finally, physical activity in subjects with CC genotype was similar in both times (122.1±11.2 min/week *vs.* 125.3±9.9 min/week: $p$=0.26). T allele carriers maintained the same physical activity (123.8±7.2 min/week *vs.* 130.1±10.2 min/week: $p$=0.30) (Table II).

As shown in Table III, the adiposity parameters and blood pressure levels were similar in both genotypes at baseline. After the pMR 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 adiposity parameters were higher in non-T allele carriers than T allele carriers. The percentage of patients who achieved 7.5% weight loss was higher in the non-T carriers (76.7% *vs.* 48.4%), with a different average of weight loss (-12.3±0.3 kg *vs.* -5.9±0.5 kg: $p$=0.01). The odds ratio to achieved 7.5% of weight loss adjusted by age and initial weight was (OR= 2.22, 95% CI=1.24-4.01; $p$=0.02). After dietary intervention, adiposity parameters were higher in subjects with T allele than non-T allele carriers.

Table IV illustrated the results in biochemical parameters. Total cholesterol, LDL- cholesterol, triglyceride, fasting insulin levels and HOMA-IR improved in both genotype groups. Moreover, after dietary intervention with the pMR hypocaloric diet, the improvement in triglyceride (CC vs. CT+TT) (-23.2±1.2 mg/dl *vs.* -15.0±2.0 mg/dl: $p$=0.01), insulin resistance as HOMA-IR (-1.5±0.3 *vs.* -0.8±0.4: $p$=0.01) and insulin levels (-6.5±1.1 UI/L *vs.* -2.1±0.8 UI/L: $p$=0.02) were higher in non T allele carriers than T allele carriers. After dietary intervention, insulin, HOMA-IR, and triglyceride levels were higher in subjects with T allele than non-T allele carriers.

## Discussion

In this study, a negative association was found between T allele of rs1121980 variant (FTO gene) and the adiposity changes and biochemical im-

**Table III.** Anthropometric parameters and blood pressure (mean ± SD).

| Parameteres | N = 219 | | | | | | *p* deltas between genotype changes *p* basal genotype *p* post treatment genotype |
|---|---|---|---|---|---|---|---|
| | CC (n = 56) | | | CT+TT (n = 163) | | | |
| | Basal | 12 weeks | *p*-value | Basal | 12 weeks | *p*-value | |
| BMI | 39.3 ± 4.3 | 36.8 ± 2.1* | $p = 0.02$ | 39.4 ± 2.1 | 37.9 ± 2.0* | $p = 0.04$ | $p = 0.02$<br>$p = 0.13$<br>$p = 0.02$ |
| Weight (kg) | 100.7 ± 4.5 | 88.4 ± 3.2$ | $p = 0.01$ | 99.1 ± 4.1 | 93.6 ± 2.1$ | $p = 0.03$ | $p = 0.01$<br>$p = 0.33$<br>$p = 0.03$ |
| Fat mass (kg) | 53.4 ± 2.1 | 38.1 ± 2.1# | $p = 0.01$ | 52.1 ± 3.0 | 49.2 ± 2.1# | $p = 0.01$ | $p = 0.03$<br>$p = 0.42$<br>$p = 0.02$ |
| WC (cm) | 118.2 ± 2.1 | 111.2 ± 2.0& | $p = 0.01$ | 117.3 ± 3.2 | 113.1 ± 2.8& | $p = 0.03$ | $p = 0.01$<br>$p = 0.32$<br>$p = 0.03$ |
| SBP (mmHg) | 131.3 ± 2.0 | 121.2 ± 2.1** | $p = 0.04$ | 132.1 ± 3.1 | 122.9 ± 4.1** | $p = 0.03$ | $p = 0.19$<br>$p = 0.28$<br>$p = 0.27$ |
| DBP (mmHg) | 83.5 ± 3.0 | 76.2 ± 2.1*** | $p = 0.03$ | 82.3 ± 3.0 | 76.9 ± 2.0*** | $p = 0.03$ | $p = 0.29$<br>$p = 0.30$<br>$p = 0.22$ |

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 deltas between both genotype groups (BMI, weight, fat mass and WC).

provements (insulin, HOMA-IR, and triglyceride levels) after a partial meal replacement (pMR) hypocaloric diet. These improvements were better in non-T allele carriers and allowed lower values at 12 weeks of treatment.

This is the first study to examine the role of rs1121980 on the effect of a pMR diet in obese subjects. Previous studies[8-11] often focused on the effect of interaction of different dietary nutrients or dietary patterns with this FTO gene variant in relation to obesity. In some studies[8-11], carriers of the risk allele of rs1121980, BMI was approximately 2-fold higher in individuals with a Western dietary pattern and waist circumference increased with increasing of wester dietary pattern score. Moreover, a cohort study[8] showed no association between the presence of risk allele and changes of anthropometric parameters over six years of follow up. Goodarzi et al[7] reported that obese subjects with the minor allele of rs1121980 had lower visceral adiposity and body mass index changed when they had higher dietary diversity score[7-9]. In other cross-sectional study[10], rs1121980 included in a genetic risk score showed that the obesity risk was decreased across quartiles of Mediterranean dietary pattern in subjects with high-risk score. Mediterranean diet adherence modulated risk of obesity in subjects with this allele risk score. In other cross-sectional study, carriers of the minor allele of this SNP did not present greater BMI than noncarriers. Moreover, authors[11] reported a higher BMI in risk allele patients than the other genotype only when they had a high-saturated fatty acid intake. Nevertheless, the biological mechanisms underlying this interaction remain unknown and it suggested that high saturated fatty acid intake instead of total fat intake may be more relevant in increasing the effect of the FTO risk allele on BMI. Finally, Hosseini-Esfahani et al[15] reported a significant interaction between total fiber intake and some SNPs of FTO including rs1121980. In summary, as we have previously reviewed, this SNP modulates the action of the oral diet on different adipocyte parameters in cross sectional designs.

**Table IV.** Biochemical parameters in both genotype groups (mean ± SD).

| Biochemical parameters | N = 259 | | | | | | p deltas between genotype changes p basal genotype p post treatment genotype |
|---|---|---|---|---|---|---|---|
| | CC (n = 56) | | | CT+TT (n = 163) | | | |
| | Basal | 12 weeks | p-value | Basal | 12 weeks | p-value | |
| Glucose (mg/dl) | 102.3 ± 2.1 | 98.6 ± 4.1 | $p = 0.25$ | 101.9 ± 1.1 | 97.9 ± 2.2 | $p = 0.28$ | $p = 0.22$<br>$p = 0.51$<br>$p = 0.23$ |
| Total cholesterol (mg/dl) | 218.1 ± 7.7 | 191.1 ± 4.2* | $p = 0.01$ | 217.9 ± 4.8 | 190.1 ± 7.1 | $p = 0.01$ | $p = 0.44$<br>$p = 0.59$<br>$p = 0.12$ |
| LDL-cholesterol (mg/dl) | 137.1 ± 5.1 | 115.0 ± 3.1$^{\$}$ | $p = 0.02$ | 136.9 ± 4.0 | 114.1 ± 3.2 | $p = 0.03$ | $p = 0.60$<br>$p = 0.70$<br>$p = 0.38$ |
| HDL-cholesterol (mg/dl) | 56.1 ± 3.0 | 54.3 ± 3.1 | $p = 0.45$ | 56.0 ± 3.1 | 54.9 ± 3.1 | $p = 0.50$ | $p = 0.31$<br>$p = 0.60$<br>$p = 0.33$ |
| Triglycerides (mg/dl) | 120.4 ± 4.1 | 97.2 ± 8.1$^{\#}$ | $p = 0.01$ | 118.1 ± 5.2 | 103.8 ± 7.1 | $p = 0.03$ | $p = 0.01$<br>$p = 0.23$<br>$p = 0.04$ |
| Insulin (mUI/l) | 15.5 ± 0.8 | 9.0 ± 1.0$^{\&}$ | $p = 0.02$ | 16.0 ± 1.1 | 13.9 ± 0.9$^{\&}$ | $p = 0.04$ | $p = 0.02$<br>$p = 0.29$<br>$p = 0.03$ |
| HOMA-IR | 4.7 ± 0.3 | 3.2 ± 0.1** | $p = 0.02$ | 4.8 ± 0.2 | 4.0 ± 0.3** | $p = 0.04$ | $p = 0.01$<br>$p = 0.39$<br>$p = 0.03$ |

HOMA-IR (Homeostasis model assessment). Statistical differences $p < 0.05$, in each genotype group (*Total cholesterol, $^{\$}$LDL-cholesterol, $^{\#}$Triglycerides, $^{\&}$Insulin, **HOMA IR). Last column: Statistical differences post-treatment values and changes between Deltas of both genotype groups (triglycerides, insulin and HOMA-IR).

Our present interventional study showed a better decrease of weight, fat mass and waist circumference with the pMR hypocaloric diet in non-T allele carriers. The pMR diet produced an intake of about 1,000 calories per day in both genotypes with a low-fat content (about 20% of the total caloric value), with a predominance of monounsaturated fats and a low percentage of saturated fats. In other words, this type of diet has a composition of macronutrients equivalent to the Mediterranean diet, and the worse response obtained in the non-T allele carriers may be related to the data of the previously analyzed literature[10].

In our study, we also observed a better metabolic response (insulin, insulin resistance and triglycerides) in non-T allele carriers. This better response can be explained, considering that when insulin resistance developed in fat tissues, insulin-mediated inhibition of lipolysis decreased too. The secondary increase in circulating free fatty acids (FFAs) in turn worsens insulin resistance by causing alterations in the insulin-signalling cascade creating a vicious cycle[16]. In addition, high levels of FFAs increased triglyceride synthesis and reduction of very-low-density lipoproteins (VLDLs)[17]. Therefore, the non-T allele carrier subjects, having a greater decrease in fat mass, would present a greater improvement in the previously mentioned biochemical parameters. Nevertheless, also there is evidence regarding the direct role of this SNP in fat distribution and insulin resistance[18]. Finally, the type of dietary fat could have a dominant role, for example in other interventional study with the variant rs9939609 of FTO gene reported different metabolic response with two different hypocaloric diets (high monounsaturated fatty acid *vs.* high polyunsaturated fatty acid)[19].

The mechanisms by which the rs1121980 variant of the FTO gene modify the metabolic and weight response to the pMR hypocaloric diet are unknown. In one study, although this genetic

variant was not associated with BMI, it was associated with the presence of diabetes mellitus[20]. However, in other studies there was a direct relationship with the presence of morbid obesity[21]. One study has even shown how this SNP modulated the association of food reinforcement with energy intake. Therefore, different metabolic and dietary pathways could be implicated to explain these findings[22].

### Limitations

The present study has limitations that need to be considered. First, the inclusion in the single-arm intervention trial of Caucasian obese subjects with low cardiovascular risk that does not allow the generalization of the results beyond a population of obese with cardiovascular comorbidities or other ethnicities. Second, we only evaluated one SNP of FTO gene, so other genetic variants of this gene could also be implied in our findings. Third, many other uncontrolled factors could influence our results (epigenetic, mental health, sleeping pattern and timing of food, for example). Finally, the self-reported dietary intake with a standardized software might include bias of under- or over-reporting energy and potential variations in nutrient compositions. The main strength of the present study includes it is a prospective design and its results come from an approximately homogeneous population.

## Conclusions

In conclusion, non-T allele carriers of rs1121980 shows a higher magnitude of weight loss and improvement in adiposity parameters resulting from a pMR diet than T allele carriers. These adiposity improvements produce a better response of insulin resistance, insulin levels and triglyceride levels. These results support genetic evaluation prior to pMR diet in order to predict the response. This fact has practical implications in a personalized nutrition treatment in obese subjects.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

### Ethics Approval

This study protocol was reviewed and approved by HCUVa Eats Health Area of Valladolid; approval number [07/2020].

### Informed Consent

Written informed consent was obtained from participants (or their parent/legal guardian/next of kin) to participate in the study.

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### Authors' Contribution

D. A. de Luis and J.J. Lopez Gomez designed the study an wrote the article. O. Izaola, and J.J. Lopez Gomez realized nutritional evaluation. D. Primo and D.A. de Luis realized biochemical evaluation.

### Data Availability

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

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