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# Effects of *C358A* missense polymorphism of the degrading enzyme fatty acid amide hydrolase on weight loss, adipocytokines, and insulin resistance after 2 hypocaloric diets

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**Abstract**

It has been demonstrated that the polymorphism 385 C/A of fatty acid amide hydrolase was associated with obesity. We decided to investigate the role of a polymorphism (cDNA 385 C->A) on insulin resistance and weight loss secondary to a low-fat vs a low-carbohydrate diet. A population of 248 patients with obesity was analyzed. Basal measurements were performed, and values were compared to those at the end of a 3-month period in which subjects received either diet I (low fat) or diet II (low carbohydrate). One hundred seventy-eight patients (71.8%) had the genotype *C358C* (wild-type group), and 70 (28.2%) patients had the genotype *C358A* (62 patients, 25%) or *A358A* (8 patients, 3.2%) (mutant-type group). With diet I, body mass index, weight, fat mass, waist circumference, and systolic blood pressures decreased in the wild-type and mutant-type groups. With diet II, body mass index, weight, fat mass, waist circumference, and systolic blood pressures decreased in both genotypes. With diet I, leptin, glucose, total cholesterol, triglyceride, insulin, and homeostasis model assessment for insulin sensitivity (HOMA) decreased in the wild-type group. In the mutant-type group, only cholesterol decreased in a significant way. With diet II, leptin, interleukin-6, glucose, total cholesterol, low-density lipoprotein cholesterol, insulin, HOMA, and C-reactive protein decreased in the wild-type genotype. The allele A358 of fatty acid amide hydrolase was associated with a lack of improvement on glucose insulin, HOMA, and leptin levels in both diets after weight loss.


## 1. Introduction

Weight reduction is known to be an effective treatment for obese patients and those who have risk factors for the metabolic syndrome [1]. However, obesity has multiple causes and is determined by the interaction between genetic and environmental factors [2].

In this scenario, the important role played by endocannabinoid system is emerging: it controls food intake, energy balance, and lipid and glucose metabolism through both central and peripheral effects, and stimulates lipogenesis and fat accumulation. Herbal *Cannabis sativa* (marijuana) has been known to have many psychoactive effects in humans including increases in appetite and body weight [3]. Nevertheless, the mechanism underlying cannabinoid neurobiological effects has been recently revealed [4]. The main inactivating enzyme of endogenous cannabinoid receptor ligands is fatty acid amide hydrolase (FAAH), which has been identified as the catabolic enzyme capable of inactivating endocannabinoids (anandamide) [5]. The pharmacologic effects of some endocannabinoids appear to be regulated by FAAH activity [6], suggesting that FAAH has the role to be a modulating enzyme for human behavior.

A missense polymorphism (cDNA 385 C->A) that predicts a substitution of threonine for a conserved proline residue at amino acid position 129 (P129T) has been described and is significantly associates with drug abuse [7]. Recently, some authors [8,9] have demonstrated that the homozygous FAAH 385 A/A genotype was associated with overweight and obesity. However, in a large study sample (5801 subjects), Jensen et al [10] were unable to find association of this polymorphism with overweight or obesity. There is only one interventional study; Aberle et al [11] have shown that carriers of the Pro129Thr mutation had a significantly greater improvement in lipid profile compared with wild type when following a low-fat diet.

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The role of genetic variation in this gene has been mentioned previously. In particular, gene defects showing no or a minor effect when expressed alone might influence the phenotype in such dietary intervention. The main objective of our study was to investigate the role of missense polymorphism (cDNA 385 C->A) of FAAH gene on insulin resistance and weight loss secondary to a low-fat vs a low-carbohydrate diet in obese patients.

## 2. Subjects and methods

### 2.1. Subjects

A population of 248 patients with obesity (body mass index [BMI] >30) was analyzed in a prospective way. These patients were recruited in a Nutrition Clinic Unit and signed an informed consent. Exclusion criteria included history of cardiovascular disease or stroke during the previous 24 months, total cholesterol greater than 300 mg/dL, triglycerides greater than 300 mg/dL, blood pressure greater than 140/90 mm Hg, fasting plasma glucose greater than 126 mg/dL, as well as the use of sulfonylurea, thiazolidinediones, insulin, glucocorticoids, antineoplastic agents, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and psychoactive medications. Local ethical committee approved the protocol.

### 2.2. Procedure

Patients were randomly allocated to 1 of 2 diets for a period of 3 months. Diet I was low in fat and provided 1500 kcal/d (53% carbohydrates, 20% proteins, 27% fats). Diet II was low in carbohydrate and provided 1507 kcal/d (38% carbohydrates, 26% proteins, 36% fats). The exercise program consisted of an aerobic exercise at least 3 times per week (60 minutes each). Weight, blood pressure, basal glucose, C-reactive protein (CRP), insulin, insulin resistance (homeostasis model assessment for insulin sensitivity [HOMA]), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, blood triglycerides, and adipocytokines (leptin, adiponectin, resistin, tumor necrosis factor [TNF]−α, and interleukin [IL]-6) levels were measured at basal time and at 3 months after treatment. A tetrapolar bioimpedance, an indirect calorimetry, and a prospective serial assessment of nutritional intake with 3-day written food records were realized at both times. Genotype of FAAH gene polymorphism was studied.

### 2.3. Genotyping of FAAH gene polymorphism

Oligonucleotide primers and probes were designed with the Beacon Designer 4.0 (Premier Biosoft International, Palo Alto, CA). The polymerase chain reaction was carried out with 50 ng of genomic DNA, 0.5 μL of each oligonucleotide primer (primer forward: 5′-ATG TTG CTG GTT ACC CCT CCT C-3′; primer reverse: 5′-CAG GGA CGC CAT AGA GCT G-3′), and 0.25 μL of each probe (wild probe: 5′-Fam-CAA AGA ATC AAG CAC TTT TCG AAA CA-BHQ-1-3′ and mutant probe: 5′-Hex-AGA ATC AAG CGC TTT TCG AAA CA-BHQ-1-3′) in a 25-μL final volume (Termociclador iCycler IQ; Bio-Rad, Hercules, CA). DNA was denatured at 95°C for 3 minutes; this was followed by 50 cycles of denaturation at 95°C for 15 seconds, and annealing at 59.3° for 45 seconds. The polymerase chain reaction was run in a 25-μL final volume containing 12.5 μL of IQTM Supermix (Bio-Rad) with hot start Taq DNA polymerase. Hardy-Weinberg equilibrium was assessed.

### 2.4. Assays

Plasma glucose levels were determined by using an automated glucose oxidase method (Glucose Analyzer 2; Beckman Instruments, Fullerton, CA). Insulin was measured by radioimmunoassay (Diagnostic Products, Los Angeles, CA) with a sensitivity of 0.5 mIU/L (reference range, 0.5-30 mIU/L) [12], and the HOMA was calculated using these values [13]. C-reactive protein was measured by immunoturbidimetry (Roche Diagnostics, Mannheim, Germany), with a reference range of 0 to 7 mg/dL and analytical sensitivity of 0.5 mg/dL. Lipoprotein (a) was determined by immunonephelometry with the aid of a Beckman array analyzer (Beckman Instruments, Brea, CA).

Serum total cholesterol and triglyceride concentrations were determined by enzymatic colorimetric assay (Technicon Instruments, New York, NY), whereas HDL cholesterol was determined enzymatically in the supernatant after precipitation of other lipoproteins with dextran sulfate-magnesium. Low-density lipoprotein cholesterol was calculated using the Friedewald formula.

### 2.5. Adipocytokines

Resistin was measured by enzyme-linked immunosorbent assay (ELISA) (Biovendor Laboratory, Brno, Czech Republic) with a sensitivity of 0.2 ng/mL and a reference range of 4 to 12 ng/mL) [14]. Leptin was measured by ELISA (Diagnostic Systems Laboratories, Webster, TX) with a sensitivity of 0.05 ng/mL and a reference range of 10 to 100 ng/mL [15]. Adiponectin was measured by ELISA (R&D Systems, Minneapolis, MN) with a sensitivity of 0.246 ng/mL and a reference range of 8.65 to 21.43 ng/mL [16]. Interleukin-6 and TNF-α were measured by ELISA (R&D Systems) with a sensitivity of 0.7 and 0.5 pg/mL, respectively. Reference values were 1.12 to 12.5 pg/mL for IL-6 and 0.5 to 15.6 pg/mL for TNF-α [17,18].

### 2.6. Indirect calorimetry

For the measurement of resting energy expenditure, subjects were admitted to a metabolic ward. After a 12-hour overnight fast, resting metabolic rate was measured in the sitting awake subject in a temperature-controlled room over one 20-minute period with an open-circuit indirect calorimetry system (standardized for temperature, pressure, and moisture) fitted with a face mask (MedGem; Health

Tech, Los Angeles, CA) (coefficient of variation, 5%). Resting metabolic rate (in kilocalories per day) and oxygen consumption (in millimeters per minute) were calculated [19].

### 2.7. Anthropometric measurements

Body weight was measured to an accuracy of 0.5 kg, and body mass index was computed as body weight/(height$^2$). Waist (narrowest diameter between xiphoid process and iliac crest) and hip (widest diameter over greater trochanters) circumferences to derive waist-to-hip ratio were measured, too. Tetrapolar body electrical bioimpedance was used to determine body composition with an accuracy of 5 g [20]. Blood pressure was measured twice after a 10-minute rest with a random zero mercury sphygmomanometer and averaged.

### 2.8. Dietary intake and habits

Patients received prospective serial assessment of nutritional intake with 3-day written food records. All enrolled subjects received instruction to record their daily dietary intake for 3 days including a weekend day. Handling of the dietary data was by means of a personal computer equipped with personal software, incorporating use of food scales and models to enhance portion size accuracy. Records were reviewed by a registered dietitian and analyzed with a computer-based data evaluation system. National composition food tables were used as reference [21]. Regular aerobic physical activity (walking was allowed, no other exercises) was maintained during the period study for at least 3 times per week (60 minutes each).

### 2.9. Statistical analysis

Sample size was calculated to detect differences of more than 2 kg in body weight with 90% power and 5% significance (n = 90 in each diet group). The results were expressed as average ± standard deviation. The distribution of variables was analyzed with Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with a 2-tailed Student *t* test. Nonparametric variables were analyzed with the Mann-Whitney *U* test. Qualitative variables were analyzed with the $\chi^2$ test, with Yates correction as necessary, and Fisher test. The statistical analysis was performed for the combined *C358A* and *A358A* as a group and wild-type *C358C* as second group. A *P* value < .05 was considered statistically significant.

## 3. Results

Two hundred forty eight patients gave informed consent and were enrolled in the study. The mean age was 43.2 ± 14.1 years and the mean was BMI 36.3 ± 5.9, with 56 men (22.6%) and 192 women (77.4%).

All subjects were weight stable during the 2-week period preceding the study (body weight change, 0.23 ± 0.1 kg). All patients completed the 3-month follow-up period. One hundred seventy eight patients (71.8%) had the genotype *C358C* (wild type group), and 70 (28.2%) patients had the genotype *C358A* (62 patients, 25%) or *A358A* (8 patients, 3.2%) (mutant-type group). Age was similar in both groups (wild type: 45.9 ± 16.3 years vs mutant group: 46.2 ± 15.8 years, not significant). Sex distribution was similar in both groups (men: 21.3% vs 25.7%, women: 78.7% vs 74.3%).

In the 127 subjects (88 wild type and 39 mutant type) treated with diet I, basal assessment of nutritional intake with a 3-day written food record showed a calorie intake of 1859 ± 681.6 kcal/d, a carbohydrate intake of 181.8 ± 68.7 g/d (40% of calories), a fat intake of 90.1 ± 33.7 g/d (39.9% of calories), and a protein intake of 95.4 ± 22.1 g/d (20.1% of calories). During the intervention, these subjects reached the recommendations of diet I (low fat: 1631 kcal/d, with 25.2% of the total calorie intake as fats).

In the 121 subjects (90 wild type and 31 mutant type) treated with diet II, basal assessment of nutritional intake with a 3-day written food record showed a calorie intake of 1887 ± 831.9 kcal/d, a carbohydrate intake of 194.1 ± 57 g/d (41.2% of calories), a fat intake of 83.2 ± 37.3 g/d (39.1% of calories), and a protein intake of 93.1 ± 28.1 g/d (19.7% of calories). During the intervention, these patients reached the recommendations of diet II (low carbohydrate: 1575 kcal/d, with 30.8% of total calorie intake as carbohydrates).

Table 1 shows the differences in anthropometric variables. With diet I (low fat), BMI, weight, fat mass, waist circumference, and systolic blood pressures decreased in the wild-type and mutant-type groups. With diet II (low carbohydrate), BMI, weight, fat mass, waist circumference, and systolic blood pressures decreased in both genotypes. There were no significant differences between the effects (on weight, BMI, waist circumference, fat mass, and systolic blood pressure) of the different diets in either group. No differences were detected among basal and posttreatment values of anthropometric variables between both genotypes.

Table 2 shows the classic cardiovascular risk factors. With diet I (low fat), glucose, total cholesterol, triglyceride, insulin, and HOMA decreased in the wild-type group. In the mutant-type group, only cholesterol decreased in a significant way.

With diet II (low carbohydrate), glucose, total cholesterol, LDL cholesterol, insulin, HOMA, and CRP decreased in the wild-type genotype. There were no significant differences between the effects (on glucose, total cholesterol, insulin, and HOMA) of the different diets in either group. No differences were detected among basal and posttreatment values of biochemical variables between both genotypes.

Table 3 shows levels of adipocytokines. In the wild-type group on diet I (low fat), leptin decreased. In the wild-type group on diet II (low carbohydrate), IL-6 and leptin decreased. In the mutant-type group, on diet I or II, values of all adipocytokines remained unchanged. There were

Table 1
Changes in anthropometric variables

| Characteristics | Diet I | | | | Diet II | | | |
|---|---|---|---|---|---|---|---|---|
| | *C358C* | | *C358A* or *A358A* | | *C358C* | | *C358A* or *A358A* | |
| | 0 time | At 3 mo | 0 time | At 3 mo | 0 time | At 3 mo | 0 time | At 3 mo |
| BMI | 35.3 ± 5.3 | 33.8 ± 5.8* | 34.9 ± 6.5 | 34.1 ± 6.1* | 36.1 ± 7.8 | 34.9 ± 7.4* | 34.9 ± 5.3 | 33.5 ± 5.4* |
| Weight (kg) | 92.2 ± 16.5 | 88.2 ± 16.6* | 92.1 ± 17 | 90.5 ± 16.6* | 94.7 ± 21 | 89.6 ± 20* | 90.2 ± 16.3 | 86.6 ± 15.7* |
| FFM (kg) | 52.5 ± 14.1 | 51.9 ± 14.6 | 52.3 ± 11 | 51.2 ± 12 | 52.1 ± 15.6 | 50.7 ± 14.9 | 50.4 ± 12.8 | 49.8 ± 9.3 |
| Fat mass (kg) | 38.1 ± 12.9 | 36.4 ± 12.3* | 39.2 ± 10.2 | 37.4 ± 12.1* | 40.8 ± 10.1 | 38.1 ± 11.7* | 39.1 ± 8.7 | 36.4 ± 9.3* |
| WC (cm) | 106.3 ± 14 | 102.6 ± 15.4* | 111.2 ± 16 | 106.7 ± 16* | 108.8 ± 15 | 103.4 ± 14* | 109.9 ± 13 | 104.1 ± 12.9* |
| WHR | 0.90 ± 0.07 | 0.88 ± 0.05 | 0.89 ± 0.1 | 0.89 ± 0.1 | 0.9 ± 0.07 | 0.88 ± 0.09 | 0.92 ± 0.1 | 0.90 ± 0.1 |
| SBP (mm Hg) | 136.3 ± 18 | 125 ± 12.9* | 142.2 ± 16 | 121.1 ± 12* | 143.4 ± 19 | 125.7 ± 16* | 144.8 ± 18 | 117.6 ± 12.5* |
| DBP (mm Hg) | 83.2 ± 9.1 | 82.2 ± 7.8 | 83.1 ± 6.5 | 83.4 ± 14.8 | 82.2 ± 11 | 81.1 ± 18.4 | 81.2 ± 6.8 | 77.5 ± 24.4 |
| RMR (kcal/d) | 2207 ± 723 | 2295 ± 528 | 2226 ± 445 | 2436 ± 514 | 2265 ± 358 | 2275 ± 439 | 2120 ± 422 | 2230 ± 656 |
| $VO_2$ c (mL/min) | 325.1 ± 63 | 363.8 ± 60 | 327.9 ± 68 | 346.6 ± 71 | 312.5 ± 81 | 310.5 ± 61 | 298.6 ± 57.3 | 313.4 ± 80 |

DBP indicates diastolic blood pressure; FFM, fat-free mass; RMR, resting metabolic rate; SBP, systolic blood pressure; $VO_2$ c, oxygen consumption; WHR, waist-to-hip ratio; WC, waist circumference.

* $P < .05$, in each genotype group with basal values. No statistical differences between genotypes in each diet or in different diet groups.

significant differences between the effects on leptin levels of the different diets in either group. Leptin levels decreased significantly in the wild-type group with both diets (diet I: 11.8% vs diet II: 19.6%, $P < .05$). No differences were detected among basal and posttreatment values of adipocytokines between both genotypes.

## 4. Discussion

The finding of this study is the association of the *C358A* and *A358A* FAAH genotypes with a lack of improvement on glucose insulin, HOMA, and leptin levels with both diets after weight loss. The low-carbohydrate diet had a better improvement in adipocytokines levels than the low-fat diet in patients in the wild-type group.

*C358A* single nucleotide polymorphism of the FAAH results is a common missense mutation producing an FAAH with defective expression [22,23]. Studies of the *C358A* variant and obesity from various authors have yielded conflicting results [8-11]. In our design, we investigated the effect of FAAH genetic variation on weight and also on metabolic parameters after 2 different hypocaloric diets and exercise. The novel finding of this study is the association of the allele A358 of FAAH with a lack of metabolic improvements in glucose metabolism after weight loss with both diets.

There were no differences among anthropometric parameters before and after dietary treatment between both genotypes. The lack of association between this polymorphism and anthropometric parameters has been described by other authors, too. The results of our study agree with those of Jensen et al [10] or Papazoglou et al [23] and contrast with those of Sipe et al [8]. These authors showed that the median BMI was significantly higher in subjects with the A385A genotype compared with the median BMI of the other subjects [9] The inconsistencies between association studies may reflect the complex interactions between multiple population-specific genetic and environmental factors [24,25]. Perhaps, these different results could be explained by dietary intakes of subjects in previous studies in the literature. These previous studies would require composition

Table 2
Classical cardiovascular risk factors

| Characteristics | Diet I | | | | Diet II | | | |
|---|---|---|---|---|---|---|---|---|
| | *C358C* | | *C358A or A358A* | | *C358C* | | *C358A or A358A* | |
| | 0 time | At 3 mo | 0 time | At 3 mo | 0 time | At 3 mo | 0 time | At 3 mo |
| Glucose (mg/dL) | 99.2 ± 17.3 | 94.1 ± 12.7* | 94.8 ± 18 | 95.2 ± 11.6 | 103.3 ± 21 | 98.5 ± 13.6* | 96.5 ± 12 | 96.4 ± 10.6 |
| Total cholesterol (mg/dL) | 201.1 ± 29 | 187.4 ± 44* | 219 ± 29 | 221 ± 36 | 192.7 ± 38 | 183.6 ± 36* | 211.6 ± 46.4 | 194.7 ± 40.4* |
| LDL cholesterol (mg/dL) | 117 ± 34 | 111 ± 46 | 135 ± 38 | 125.7 ± 30 | 117.1 ± 39 | 111.6 ± 38* | 125.8 ± 34 | 101.7 ± 27* |
| HDL cholesterol (mg/dL) | 52.1 ± 14.6 | 50.4 ± 12.5 | 51.6 ± 16 | 49.6 ± 12.8 | 56.3 ± 13.1 | 55.4 ± 19 | 59.4 ± 18 | 56.8 ± 12.6 |
| TG (mg/dL) | 142.6 ± 70 | 118.3 ± 42* | 130.4 ± 48 | 124.5 ± 39 | 113.1 ± 53 | 107.8 ± 40 | 98.1 ± 58 | 107.9 ± 56 |
| Lp (a) (mg/dL) | 25.7 ± 27.3 | 23.9 ± 27 | 25.4 ± 22 | 20.9 ± 28 | 38.9 ± 44 | 42.7 ± 55 | 41.3 ± 40.3 | 36.4 ± 55.4 |
| Insulin (mIU/L) | 18.3 ± 10.9 | 13.8 ± 6.8* | 13.6 ± 11.8 | 14.9 ± 5.9 | 17.9 ± 14 | 12.7 ± 6.9* | 13.5 ± 8.6 | 11.1 ± 7.1 |
| HOMA | 4.8 ± 4.6 | 3.3 ± 1.6* | 4.4 ± 4.3 | 3.4 ± 1.9 | 4.8 ± 5.2 | 3.1 ± 1.4* | 3.2 ± 2.3 | 2.8 ± 1.6 |
| CRP (mg/dL) | 5.6 ± 5.5 | 5.5 ± 3.4 | 4.9 ± 5.4 | 5.2 ± 3.1 | 5.7 ± 5.5 | 4.5 ± 4.2* | 4.9 ± 5.1 | 3.9 ± 3.8 |

Lp (a) indicates lipoprotein (a); TG, triglycerides.

* $P < .05$, in each group with basal values. No statistical differences between genotypes in each diet or in different diet groups.

Table 3
Circulating adipocytokines

| Characteristics | Diet I | | | | Diet II | | | |
|---|---|---|---|---|---|---|---|---|
| | *C358C* | | *C358A or A358A* | | *C358C* | | *C358A or A358A* | |
| | 0 time | At 3 mo | 0 time | At 3 mo | 0 time | At 3 mo | 0 time | At 3 mo |
| IL-6 (pg/mL) | 2.1 ± 2.3 | 2.5 ± 2.8 | 1.9 ± 2.3 | 2.1 ± 3.2 | 5.5 ± 2.9 | 2.5 ± 3.9* | 2.1 ± 2.2 | 3.2 ± 2.6 |
| TNF-α (pg/mL) | 6.8 ± 4.8 | 6.6 ± 5.1 | 5.9 ± 4.7 | 6.5 ± 5.4 | 5.8 ± 4.2 | 5.9 ± 4.8 | 5.7 ± 4.3 | 6.6 ± 4.6 |
| Adiponectin (ng/mL) | 47.9 ± 26.9 | 37.4 ± 29.3 | 37.8 ± 36 | 32.8 ± 41 | 41.8 ± 43.2 | 38.4 ± 36.2 | 54.7 ± 25 | 50.2 ± 13.3 |
| Resistin (ng/mL) | 3.9 ± 2.4 | 4.1 ± 2.1 | 3.1 ± 2.2 | 2.9 ± 1.4 | 3.6 ± 1.5 | 3.5 ± 1.6 | 3.3 ± 1.6 | 3.2 ± 1.2 |
| Leptin (ng/mL) | 85.7 ± 75 | 75.6 ± 51* | 85.5 ± 80 | 79 ± 70 | 103.7 ± 64 | 83.3 ± 60* | 91.9 ± 76 | 86.9 ± 80 |

* $P < .05$, in each group with basal values. No statistical differences between genotypes in each diet or in different diet groups.

analysis of the dietary intakes. In our study, dietary intake was controlled; and it was an interventional variable with different response in both genotype groups.

Some evidence indicates that the endogenous cannabinoid system is an essential homeostatic regulator of weight via central appetite-stimulating mechanisms as well as peripheral lipogenesis [25,26]. An association between this polymorphism and metabolic profile has been described previously. Interestingly, Aberle et al [11] have shown that carriers of the A allele had a significantly greater decrease in the total cholesterol and triglycerides as compared with wild type when following a low-fat diet. Our results did not show these results. A significant decrease in total cholesterol and LDL cholesterol levels in mutant and wild-type groups was detected with a low-carbohydrate diet; but low-fat diet decreased only glucose, HOMA, and insulin levels in the wild-type group without effects on the mutant-type group. As we can see, macronutrient distribution is a main point in the interaction between weight loss and metabolic response. According to other studies [9], the A allele of FAAH encodes a functionally deficient protein, expressing about half the enzymatic activity as the wild type. Because FAAH is the major anandamide degrading protein, a functionally less active protein may lead to an increased hepatic and central endocannabinoid concentration resulting in an up-regulation of energy storage. Under a hypocaloric diet, this up-regulation could decrease in a higher way in mutant-type genotype patients than patients with wild-type genotype and thereby could result in the observed improvement in metabolic profile.

In our study, the improvement on levels of glucose, insulin, and HOMA in the wild-type group with both diets could be related with a decreased postprandial response of fatty acids absorption (not measured in our design). Decreased free fatty acids decrease the accumulation of triglycerides in the adipocyte, related with imbalance of lipoprotein lipase activity and underproduction of proinflammatory markers. The lack of association of this anti-inflammatory state with fat mass or BMI in the mutant-type group could indicate the existence of complex unmeasured gene-gene or gene-environment interactions that may enhance metabolic abnormalities in obese patients.

In conclusion, the allele A358 of FAAH was associated with a lack of improvement on glucose insulin, HOMA, and leptin levels in both diets after weight loss. The low-carbohydrate diet had a better improvement in adipocytokines levels than the low-fat diet in patients in the wild-type group. Metabolic modifications secondary to weight loss after altering dietary advice in obese patients could be influenced by this polymorphism; further studies are needed to explore this interesting area.

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