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Correlation between Lingual *CD36* Gene Polymorphism (AA), Eating Disorder and Obesity in Algerian Adolescents

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Abstract

Background: Altered lipid perception might influence obesity risk by affecting feeding behavior. The goal of the present study was to compare eating habits between adolescents with AA polymorphism of *CD36* gene with their obese and lean counterparts.

Methods and Findings: The study population (n=165, age=13.9 ± 1.1 years) was divided into two groups. One was composed of 65 adolescents with AA genotype of *CD36* lingual gene (35 obese, 30 control), 76 adolescents with AG genotype (43 obese, 33 control) and 24 adolescents with GG genotype (5 obese, 19 control). The other was composed of 83 adolescents with obesity (z-score 2.67 ± 0.29, 14.01 ± 0.19 years) and 82 without obesity (z-score 0.03 ± 0.0, 13.92 ± 0.23 years). The BMI z-score, oleic acid sensitivity test and eating habits were assessed in all subjects. Adolescents with AA genotype of *CD36* lingual gene had the same eating habits than adolescents with obesity without AA genotype in terms of eat-containing products consumption (meat in general, sausages and offal), French fries, milk and soda (p<0.05). We also demonstrated an opposite trend in fruits and candies intake. Eating habits of adolescents with AA-allele of *CD36* gene polymorphism are similar to those of adolescents with obesity in foods containing fat, which may explain the increase in detection threshold for emulsions containing fatty acids in subjects with obesity.

Conclusion: The AA genotype of the *CD36* gene and the higher detection threshold for fatty acids may play a significant role in eating disorder and the development of obesity in our population of Algerian adolescents.

Keywords: Adolescent; Obesity; *CD36* polymorphism; Fat detection threshold; Eating habits

Introduction

Obesity and overweight in adolescents are reaching important proportions in the whole world and raise a large interest in the world health research. Indeed, 70%-80% of adolescents with obesity will remain obese at adult age which increases morbidity risk [1]. Moreover; adolescence is a vulnerable period including puberty, where many metabolic, hormonal, psychological and behavioral disorders promote weight and fat gain [2].

Obesity is a complex disease and is mainly affected by behavioral determinants partly genetically determined including reduction in physical activity [3,4], and alimentary disorders [5,6]. In addition, heritability of obesity is between 40%-70%. Other studies demonstrated that rodents and humans could detect long-chain fatty acids, present in their diet, as gustatory cue [7,8]. The *CD36* protein, known as fatty acid translocase, or GPR120, is a G protein-coupled receptor which been shown to act as receptor in the tongue involved in the detection of dietary fatty acids. Indeed, mice lacking the expression of GPR120 lose the spontaneous preference for solutions containing oily emulsions [7,9].

The intake of dietary fats is one of the main factors involved in the development of obesity because of their high energy density, palatability and slight effect on satiety [10]. This fats

intake might be influenced by their gustatory detection. Indeed, studies in humans reported that variations in sensitivity to fatty acid taste influence the consumption of fat and then predisposition to obesity [7,11]. Besides, subjects with obesity have been shown to exhibit lower oral sensitivity for a dietary fatty acid than lean subjects and hypersensitivity to the taste of oleic acid (C18:1) was associated with decreased consumption of dietary fats and low BMI [12,13]. These results suggest that altered fats perception might influence obesity risk by affecting feeding behavior in adolescents.

In humans, the single nucleotide *CD36* gene polymorphism (rs1761667 or AA), resulting in its decreased expression, is responsible for an increase in the detection threshold for oral fatty lipids in some subjects with obesity [14]. Other authors shed light on the association of *CD36* gene polymorphism with oro-sensorial detection of high-fat foods and obesity in African-American adults [15]. By employing a self-reported taste test, these investigators observed that participants with the AA genotype had greater perceived creaminess, regardless to fat concentration of salad dressings. Later on, authors used *CD36* gene polymorphism and showed that some of subjects with obesity and with the AA genotype exhibited higher oral detection thresholds for fats than subjects with AG and GG genotypes [14]. These novel findings, available only in subjects with obesity, are changing our view on the understanding of pathogenesis of obesity. A recent study conducted in young lean and obese Algerian children showed that *CD36* gene AA polymorphism was present both in young lean and in obese children and associated with high threshold for fatty acid taste sensitivity in children with obesity only [16]. In our study conducted in 165 Algerian adolescents [17], we found that adolescents with obesity exhibited a significantly higher detection threshold (lower sensitivity) of oleic acid compared to age-matched lean participants. Moreover, we found that A-allele frequency of rs1761667 polymorphism of the *CD36* gene was higher in obese than in lean participants and was associated with a higher consumption in French fries in obese adolescents only. Our results suggest that fat-containing products might influence fats gustatory detection leading, in long term, to alimentary disorders and predisposition to obesity.

The goal of the present study is to compare eating habits between Algerian adolescents with AA, AG and GG polymorphisms of the lingual *CD36* gene with their obese and lean counterparts.

Materials and Methods

Subjects

Male and female adolescents (n=165; age=13.9 ± 1.1 years) from Constantine, district in Algeria, were enrolled in the study. The exclusion criteria were any history of a chronic pathology such as cardiovascular disease, diabetes, liver, or kidney disease. The smokers were also excluded from the study.

Ethics

The study was carried out in accordance with the Declaration of Helsinki of 1975 (as revised in 2008) of the World Medical Association, and the research council of the University of Constantine 1 approved the study protocol (10 September 2014, number of agreement: 683). Our experimental protocol conforms to the relevant ethical guidelines for human research. The material used has been validated by the National Agency for the Safety of Medicines and Health Products.

BMI z-score and eating habits

The BMI of adolescents was calculated as per WHO guidelines and expressed as z-score [18]. The lean subjects had BMI z-score below 1 and with obesity more than 2 (0.03 ± 0.00 and 2.67 ± 0.29 respectively, $p<0.01$). To observe a clear difference between lean and obese groups, the subjects with a BMI z-score between 1 and 2 were excluded from the study. To determine eating habits, the adolescents were asked to fill the feeding pattern questionnaire that consisted of 17 questions corresponding to 17 different types of food and beverages. The subjects answered how often they consumed a particular product on a rating scale from 1 to 4 (1-never, rarely; 2-once a week/month; 3-a few time each week; 4-every day). After data collection, we calculated the mean consumption frequency in our experimental population considering that never, rarely=1 point; one a week/month=2 points; a few time each week=3 points and every day=4 points.

Oleic acid sensitivity test

We used the alternative-forced choice (AFC) method as described before [16]. Briefly, different concentrations of oleic acid (OA) (0.018, 0.18, 0.37, 0.75, 1.5, 3, 6, and 12 mmol/L) were prepared and the adolescents were subjected to taste, one-by-one, the three solutions. One solution contained OA with acacia gum (0.01%) and the other two served as controls with 0.01% acacia gum only. The taste sessions were performed in an isolated chamber close to the laboratory. Control samples were prepared in the same way but without added oil. We started with the lowest OA concentration and the detection threshold was established when the subject identified twice the same solution containing OA. The participants were asked to use a nose clip to minimalize olfaction cues during the test and to rinse the mouth between every tasting. The adolescents were not allowed to drink the solutions; rather they had to spit them out after keeping the solution in mouth for few seconds.

Determination of genotype in adolescents

The DNA (*gDNA*) was extracted from venous blood, using Wizard Genomic DNA Purification Kit (Promega, USA). The Rs1761667 polymorphism of *CD36* gene was genotyped using PCR-RFLP. The *gDNA* was amplified with Kapa mix, containing Taq polymerase (Kapa Biosystems, Wilmington, MA, USA) with forward and reverse primers (5'-CAA AAT CAC AAT CTA TTC AAG ACCA-3' and 5'-TTT TGG GAG AAA TTC TGA AGA G-3'). After amplification, the 190 bp PCR product was digested by HhaI endonuclease (Thermo Fisher Scientific, Waltham, MA, USA)

which cleaves the product into two fragments of 138 bp and 52 bp if the G-allele is present, whereas in the presence of A-allele we observed undigested 190 bp products. The final products were separated and analyzed in 2% agarose gel electrophoresis, stained with ethidium bromide.

Statistical analysis

Statistical analysis has been conducted by Statistica 14 software (Statsoft, USA). Two-way ANOVA with repeated measures was used to compare the difference between parameters in the study groups. For correlations between various parameters, Spearman rank correlations were performed. Hardy-Weinberg Equilibrium (HWE) has been assessed by chi-square (χ^2) test. For the comparison of allelic and genotype frequencies between adolescents with obesity and their lean peers we used a Fisher exact test. All data are expressed as means ± SEM and $p<0.05$ was considered as statistically significant.

Results

Characteristics of the study population

Adolescents (n=165) were divided into two groups of study. The first group was divided in 3 subgroups: A group of 65 adolescents with the AA genotype (35 obese and 30 lean), a group of 76 of adolescents were with the AG genotype (43 obese and 33 lean) and a group of 24 adolescents with the GG genotype (5 obese and 19 lean) of the *CD36* lingual gene. The second group was divided into 2 subgroups. Eighty three (83) adolescents with a BMI z-score higher than 2 (females=39, males=44, z-score 2.67 ± 0.29 and 14.01 ± 0.19 years respectively) and 82 adolescents with a BMI z-score below 1 (females=37, males=45, z-score 0.03 ± 0.0, 13.92 ± 0.23 years respectively). The average age of the global population was 13.9 ± 1.1 years.

Oleic acid sensitivity and *CD36* genotyping

We observed statistically significant difference in oleic acid oral detection threshold between obese and lean adolescents. Adolescents with obesity exhibited almost twofold oleic acid detection threshold than lean participants (2.57 ± 0.29 *vs.* 1.33 ± 0.15 mmol/L, $p<0.01$ respectively). We did not observe any deviation from Hardy-Weinberg Equilibrium in lean (χ^2= 2.67) and obese (χ^2= 3.05) participants in genotype frequencies of AA of the *CD36* gene. The frequencies of AA-allele in lean and obese groups were 56.7% and 68.1% respectively ($p<0.05$, OR (Odd Ratio)=1.63; 95% CI (Confidence Interval) of OR=1.04–2.55). AA and AG genotypes were predominantly present in adolescents with obesity compared to lean adolescents (42.2% *vs*. 36.6%, $p<0.008$ and 51.8% *vs*. 40.2%, $p<0.002$, respectively). In addition, the GG genotype was less frequent in adolescents with obesity compared to lean subjects (6.0% *vs*. 32.2%, $p<0.001$, respectively). We did not find any significant differences between *CD36* genotypes and oleic acid oral sensitivity threshold. Similarly, we did not observe any significant differences between *CD36* genotypes and BMI z-score neither in lean participants nor in adolescents with obesity (p=0.58 and p=0.41 respectively). We did not find any significant differences between genders.

Eating habits between lean and obese Algerian adolescents

The mean consumption frequency of fat-containing products (i.e. French fries, meat, sausage and offal, $p<0.01$) was significantly higher in adolescents with obesity than their lean peers **(Supplementary Table S1)**. However, the mean consumption frequency of milk was lower in subjects with obesity than in lean participants ($p<0.01$) **(Supplementary Table S1)**. We also noticed a higher mean consumption frequency of soda in adolescents with obesity compared to lean subjects ($p<0.05$) **(Supplementary Table S1)**. Participants with obesity had a higher mean consumption frequency of fruits than lean participants ($p<0.05$) **(Supplementary Table S1)**. The mean consumption frequency of starchy food and bread was lower in adolescents with obesity than in lean adolescents ($p<0.01$) **(Supplementary Table S1)**. The mean consumption frequency of candies was lower in participants with obesity compared to lean ones ($p<0.05$) **(Supplementary Table S1)**.

Eating habits between Algerian adolescents with AA, AG and GG polymorphisms of the *CD36* lingual gene

The mean consumption frequency of fat-containing products (i.e. French fries, meat, sausage and offal) was not significantly different between adolescents with the AA *CD36* gene polymorphism and those with AG and GG *CD36* gene polymorphisms **(Supplementary Table S2)**. However, the mean consumption frequency of soda was significantly higher in adolescents with AA genotype than in adolescents with AG and GG *CD36* gene polymorphisms ($p<0.05$) **(Supplementary Table S2)**. We also noticed a higher mean consumption frequency of candies among adolescents with AA *CD36* gene polymorphism.

Discussion

The origin of obesity is multifactorial and eating behaviors has a significant role in this worldwide health concern. Recently, compelling evidences on fat taste, suggested that dietary lipids can be sensed by oro-gustatory system [7,8]. The *CD36* protein has a high affinity receptor for fatty acids and it seems to have a role in fatty acid detection [19]. The importance of the *CD36* gene has been exemplified in a recent study linking variants of this gene with oral fat perception and ultimately intake of dietary fat [15]. The present study is the first one to compare eating habits between Algerian adolescents with AA, AG and GG allele polymorphisms of *CD36* lingual gene with their lean and obese peers.

In our study, AA-allele frequency of *CD36* gene polymorphism was higher in adolescents with obesity than in lean participants [17]. We notably demonstrated that adolescents with obesity had a significant higher mean consumption frequency of the meat-containing products, French fries and soda than lean adolescents. Our results corroborated with other results, which showed a positive association between meat consumption and

risk for obesity in an American population [20]. Meat and especially processed one, is rich in saturated fatty acids and cholesterol [21], and its overconsumption has been associated with high BMI [22]. Rouhani et al. also reported a direct association between consumption of red or processed meat intake and obesity, high BMI and waist circumference [23]. We further observed that adolescents with the AA-allele *CD36* gene polymorphism exhibited the same eating habit concerning meat-containing products than adolescents with AG- and GG-allele *CD36* gene polymorphisms. We also observed that adolescents with A-allele of *CD36* gene polymorphism and obese adolescents had a higher mean consumption frequency of French fries than other polymorphism alleles and control participants. Our results agreed with other findings observing that consumption of high energy food including French fries contributes to weight gain and increases the risk of obesity in young children [24] and pointed out the potential role of *CD36* gene polymorphism in this condition. This previous finding is of importance since fat-containing products might influence, in the long-term, the fatty acid oro-sensory detection capacity. Our hypothesis is supported by the observations of Stewart et al. who reported that feeding a high-fat diet significantly increased oleic acid oral detection threshold in lean subjects [25]. In addition, these authors also concluded that hyposensitive subjects consumed significantly more energy, fat, saturated fat, fatty foods, had greater BMI and were lesser perceptive of small changes in the fat content of custard, compared with hypersensitive lean subjects [13]. Similarly, feeding a high-fat diet in mice resulted in high oro-sensory threshold for linoleic acid [26] suggesting that lipid perception may be involved in the development of obesity in adolescents.

Moreover, Stewart et al. showed that the BMI was correlated with high thresholds detection of long-chain fatty acids in adult obese subjects [13]. It is possible that high-fat diet in adolescents with obesity will result in increased thresholds. We can presume that as a result of low sensitivity (high detection thresholds) to fatty acids, there would be excess fat intake in adolescents with obesity, and high amounts of fatty acids would be required to elicit a response within taste receptor cells, thus contributing to excess energy intake and increasing obesity. We also observed that adolescents with the AA-allele *CD36* gene polymorphism exhibited a higher consumption frequency of soda (i.e. sweetened lemonade) than those with the AG- and GG-alleles *CD36* gene polymorphisms. Interestingly the same eating habit was observed between our adolescents with obesity and lean adolescents, which corroborates other findings [27,28] and allow us to suggest that AA-allele *CD36* gene polymorphism can lead to childhood obesity [27,28] and the development of cardiovascular diseases [29] given the same dietary habit. We also showed that adolescents with obesity had a higher mean consumption frequency of fruits than lean ones. This surprising higher rate of consumption of fruits might protect them from obesity-related complications by providing them vitamins and polyphenols [30]. We also demonstrated that adolescents with obesity had a lower consumption frequency of candies than lean adolescents and that subjects with AA-allele polymorphism of *CD36* gene had a tendency to consume more frequently candies than adolescents with AG and GG genotypes. Hence, we do not determine the real calories of the candies but the presence of cocoa in the chocolates has been shown to modulate weight gain by several mechanisms, including the decreases in the expression of genes involved in the synthesis of lipids [31]. This latter point may partly explain the higher frequency of AA genotype in our obese adolescent population.

Finally, as we identified particular eating habit in adolescents with the *CD36* gene polymorphism (i.e. high frequency consumption of meat- and fat-containing products), it would be interesting to test the addition of extracts of different plants from the Algerian pharmacopoeia which have a high affinity agonist (i.e. taste enhancers) to mimic the action of "fake fat" without bringing additional calories in this products and evaluate their potential to treat pathologies related to obesity. Moreover, knowing this specific eating habit in our Algerian adolescents, it would be easier in the future to control their eating habits regarding the high level of pesticides exposure when eating identified products like meat- and fat-containing agricultural products. This last point is in line with a new concept that tries to help conduct health risk assessment regarding unwanted chemicals in agricultural foods by a precise control of eating habit. In fine, this may improve the regulatory process of small pesticide maximum residue limits based on body weight and foods consumption to protect Algerian adolescent's health [32].

Study Limitations

Participants with obesity frequently exhibiting the AA-allele *CD36* gene polymorphism, were not associated with high oro-detection threshold for the fatty acid. However, we could not rule out an influence of altered levels of sex hormones in obese adolescents on fat taste perception and other parameters. It was also difficult to determine whether oral fat perception sensitivity affected fat intake or body weight regulation.

Conclusion

Considering the results of the present study, eating habits of adolescents with the AA-allele of the *CD36* lingual gene were similar to those of adolescents with obesity. In addition, the mean consumption frequency of meat-containing products, French fries, milk and soda was also similar between these two groups of adolescents. Finally, our results allow us to infer that eating habits and particularly the intake of foods containing fats, in adolescents with the AA genotype of the *CD36* lingual gene were similar to those of adolescents with obesity. This result may explain the increase in the detection threshold for emulsions containing fatty acids in subjects with obesity and suggest an "obesity behavior" in adolescents with the AA-allele *CD36* lingual gene polymorphism.

Supplementary Information

http://www.imedpub.com/supplementary-file/2572-5394-3-S1006s.pdf

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Competing and Conflicting Interests

No competing and conflicting interests exist.

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