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Original article

rs6923761 gene variant in glucagon-like peptide 1 receptor: Allelic frequencies and influence on cardiovascular risk factors in a multicenter study of Castilla-Leon

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SUMMARY

Background: Some GLP-1 receptor studies have identified polymorphisms in the GLP-1 receptor gene that might be related to different cardiovascular risk factors.
Objective: Our aim was to investigate the allelic distribution of rs6923761 *GLP-1 receptor* polymorphism in a geographic area of Spain (Community of Castilla y Leon) and to evaluate the influence of this polymorphism on obesity anthropometric parameters and cardiovascular risk factors in the fasted state in obese patients.
Design: A sample of 341 obese subjects (body mass index $\geq$ 30 kg/m^2) was analyzed. Fasting blood glucose, C-reactive protein (CRP), plasma insulin, insulin resistance (HOMA-IR), and lipid profile were determined. Anthropometric parameters, dietary intake and blood pressure were recorded.
Results: One hundred and forty three patients (42.0%) had the genotype GG (wild-type group) and one hundred and ninety eight (58.0%) patients were A carriers: GA (164 patients, 48.1%) or AA (34 patients, 9.9%) (mutant-type group). Valladolid and Segovia health areas had the lowest percentage of wild type genotype and G allelic (than other Health Areas). Burgos Health Area had a higher percentage of wild-type genotype. In wild-type group (GG genotype), BMI (0.9 $\pm$ 1.3 kg/m^2; $p < 0.05$), weight (3.3 $\pm$ 1.1 kg; $p < 0.05$), fat mass (2.5 $\pm$ 1.1 kg; $p < 0.05$), waist to hip ratio (0.02 $\pm$ 0.005 cm; $p < 0.05$), waist circumference (2.8 $\pm$ 1.1 cm; $p < 0.05$), triglycerides (14.4 $\pm$ 3.3 mg/dl; $p < 0.05$) insulin (3.1 $\pm$ 1.0 mg/dl; $p < 0.05$) and HOMA-IR (1.2 $\pm$ 0.9 mg/dl; $p < 0.05$) were higher than A allele carriers. In non A allele carriers, lower HDL cholesterol levels than A allele carriers (6.4 $\pm$ 2.3 mg/dl; $p < 0.05$) were found.
Conclusion: Data from our study revealed different allelic distribution in this geographic area, with better parameters (Body mass index, weight, fat mass, waist circumference, triglycerides, insulin, HOMA-IR and HDL cholesterol) in A allele carriers than in non A allele carriers.
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1. Introduction

Glucagon-like peptide-1 (GLP-1) is a well-known neuro-enteroendocrine hormone that plays a physiological role in maintaining blood glucose levels, dietary intake and other metabolic actions [1]. This hormone is synthesized by L-cells localized in the mucosa of the ileum/colon. The time sequence is as follows; after food ingestion, GLP-1 is secreted into the blood circulation from ileal cells and acts on different tissues (brain, pancreatic islets, heart, kidney and gastrointestinal tract) in order to attenuate the postprandial rise in blood glucose levels after food intake rich in carbohydrates. The mechanisms to control glucose levels are the improvement of glucose-induced insulin secretion, the stimulation of insulin-producing beta cells growth, the delay of gastric emptying -thereby reducing postprandial glucose excursions- and to decrease appetite in order to stop food intake [2].

Abbreviations: BMI, body mass index; GLP-1-R, glucagon like peptide 1 receptor; HOMA-IR, homeostasis model assessment; CRP, C reactive protein.

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GLP-1 performs these actions via a G-protein-coupled receptor (GLP-1R) that it is located in pancreatic islets, lung and brain [3]. The receptor is a 463 amino acid long and contains 7 transmembrane domains belonging to a family of G-protein coupled receptors [4]. Some studies of the GLP-1R have identified polymorphisms in the GLP-1R gene that may be related to pathogenesis of diabetes mellitus, obesity and to modulation of response to different diabetic drugs [5]. For example, a study of individuals with type 2 diabetes mellitus identified a patient with a heterozygous GLP-1R missense polymorphism that resulted in substitution of threonine 149 by methionine (T149M) (RS112198) [6]. In other study [7], it has been showed that the T149M substitution produces a significant loss of function of this receptor. In another study [8], two different genetic variations in GLP1R (rs6923761) and (rs3765467) decreased binding affinity and reduced insulin secretion following GLP-1 infusion in non-obese subjects. The genetic variant of GLP1-R rs6923761 are the most frequent of all studied variants and it is a target to evaluate the effect of this genetic variants of this receptor on basal metabolic factors [9], metabolic syndrome [10], weight loss after dietary interventions [11] or different interventions such as bariatric surgery [12] and diabetic drugs [5].

The high prevalence of this polymorphism and the little evidence in this topic area, pushed us to investigate the allelic distribution of rs6923761 *GLP-1 receptor* polymorphism in a geographic area of Spain (Community of Castilla y Leon) and to evaluate the influence of this polymorphism on obesity anthropometric parameters and cardiovascular risk factors in the fasted state in obese patients.

1.1. Subjects

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and the local ethics committee of our Hospital approved all procedures involving patients. All participants provided signed informed consent.

A sample of 341 Caucasian obese (body mass index > 30) subjects was analyzed in a prospective way. The recruitment of subjects was a non-probabilistic method of sampling. Obese Patients were referred from Primary Care Physicians to the Units of Nutrition of each Health Area of Castilla y Leon in the Northwest of Spain (Avila ($n = 156{,}535$ habitants), Burgos ($n = 350{,}122$ habitants), Leon ($n = 473{,}407$ habitants), Palencia ($n = 165{,}740$ habitants), Salamanca ($n = 335{,}407$ habitants), Segovia ($n = 141{,}750$ habitants), Soria ($n = 90{,}521$ habitants), Valladolid ($n = 507{,}297$ habitants), Zamora ($n = 182{,}710$ habitants)). Inclusion criteria were body mass index ≥ 30 kg/m^2 and absence of weight reducing diet during the 3 months prior to the study. Subjects were excluded if history of cardiovascular disease or stroke during the previous 24 months, total cholesterol > 200 mg/dl, triglycerides > 200 mg/dl, blood pressure > 140/90 mmHg, fasting plasma glucose > 126 mg/dl, or use of sulphonyl urea, thiazolidinediones, insulin, glucocorticoids, antineoplastic agents, angiotensin receptor blockers, angiotensin converting enzyme inhibitors, psychoactive medications and a hypocaloric diet in previous 12 months.

1.2. Procedure

Whole blood samples were drawn after overnight fasting (10 h). Weight, blood pressure, basal glucose, c-reactive protein (CRP), insulin, insulin resistance (HOMA-IR), total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides were determined. Also, a bioimpedance and a prospective serial assessment of nutritional intake of the previous 3 days were performed on the same day. Genotype of rs6923761 *GLP-1 receptor* gene polymorphism was studied.

1.2.1. Genotyping of rs6923761 GLP-1 receptor gene polymorphism

Oligonucleotide primers and probes were designed with the Beacon Designer 5.0 (Premier Biosoft International®, LA, CA). The polymerase chain reaction (PCR) was carried out with 50 ng of genomic DNA, 0.5 μL of each oligonucleotide primer (primer forward: 5′-GTTCCTCTACATCATCTACAC-3′ and reverse 5′-CTGCTTCATTCCTCTATCTG-3′ and 0.25 μL of each probes (wild probe: 5′-Fam-CGATCCTCCTCGGCTTCAGGTA-BHQ-1-3′) and (mutant probe: 5′-Texas red-CGATCCTCCTCAGCTTCAGGTA-BHQ-2-3′) in a 25 μL final volume (Termociclador iCycler IQ (Bio-Rad®), Hercules, CA). DNA was denaturated at 95 °C for 3 min; this was followed by 45 cycles of denaturation at 95 °C for 15 s, and annealing at 58.1°°C for 45 s). The PCR were run in a 25 μL final volume containing 12.5 μL of IQTM Supermix (Bio-Rad®, Hercules, CA) with hot start Taq DNA polymerase. The probes are irradiated with a blue light emitting diode (470 nm), which excites yellow fluorophores including fluorescein (FAM probe). In genetic material of wild type subjects, only yellow fluorophores are excited because the two strands of DNA are labeled with FAM. If one of the strands does not emit light it is heterozygous mutant and if neither of the two strands emits it is homozygous mutant. Both (homozygous and heterozygous mutant; AA + GA) were called (mutant type group) and the analysis was realized in a dominant model. The wild type group was formed by subjects with GG genotype Hardy Weimberg equilibrium was assessed with a statistical test (Chi-square) to compare our expected and observed counts. The variant were in Hardy Weimberg equilibrium ($p = 0.34$).

1.3. Assays

Plasma glucose levels were measured by using a glucose oxidase method (Glucose analyser 2, Beckman Instruments, Fullerton, California). Insulin was measured by radioimmunoassay (RIA Diagnostic Corporation, Los Angeles, CA) with a sensitivity of 0.5 mUI/L (normal range 0.5–30 mUI/L) [13] and the homeostasis model assessment for insulin resistance (HOMA-IR) were calculated using these using this formula (fasting insulin × fasting glucose concentrations/22.5) [14]. Serum total cholesterol and triglyceride concentrations were determined by enzymatic colorimetric assay (Technicon Instruments, Ltd., New York, N.Y., USA), while HDL cholesterol was determined enzymatically in the supernatant after precipitation of other lipoproteins with dextran sulfate-magnesium. LDL cholesterol was calculated using Friedewald formula [15]. CRP was determined by immunoturbimetry (Roche Diagnostics GmbH, Mannheim, Germany), with a normal range of (0–7 mg/dl) and analytical sensitivity 0.5 mg/dl.

1.4. Anthropometric measurements and blood pressure

Body weight was measured to an accuracy of 0.1 kg and body mass index computed as body weight/(height^2). Waist and hip circumferences to derive waist to hip ratio (WHR) were measured, too. Tetrapolar body electrical bioimpedance was used to determine body composition with an accuracy of 50 g [16] (Akern, EFG, Italy). After introduction of an 800 μA (50 kHz) excitation current, BIA measures the geometrical components of electrical impedance Z_c, i.e., resistance R (the sum of in phase vector) and the capacitive component, reactance X (the sum of out-phase vectors) derived from $Z^2 = R^2 + X_c^2$. Precautions taken to insure valid BIA measurements were; no alcohol within 24 h of taking the test, no exercise or food for 4 h before taking the test. Blood pressure was measured twice after a 10 min rest with a random zero mercury sphygmomanometer, and averaged (Omrom, LA, CA).

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1.5. Dietary intake and habits

All enrolled subjects received instruction for recording their daily dietary intake of the previous three days including a weekend day. Handling of the dietary data was made by means of a personal computer equipped with personal software, incorporating the use of food scales and models to enhance portion size accuracy. Records were reviewed by a dietitian and analyzed with a computer-based data evaluation system with national composition food tables [17] (Dietosource®, Geneva, Switzerland).

1.6. Statistical analysis

Sample size was calculated to detect differences for one kg of weight with 90% power and 5% significance ($n = 300$). The results were expressed as average ± standard deviation. The distribution of variables was analyzed with the Kolmogorov–Smirnov test. Quantitative variables with normal distribution were analyzed with a two-tailed, paired Student's-*t* test. Non-parametric variables were analyzed with the U-Mann Whitney test. ANOVA test with Bonferroni post hoc test was used with quantitative variables with more than two groups. Qualitative variables were analyzed with the chi-square test, with Yates correction as necessary, and Fisher's test. The statistical analysis was performed for the combined GA and AA as a group (mutant genotype) and wild type GG as second group (wild genotype), with a dominant model. A *p*-value under 0.05 was considered statistically significant.

2. Results

Three hundred and forty one patients signed informed consent and were included in the study. The mean age was 41.8 ± 13.1 years and the mean BMI was 37.1 ± 6.0. Sex distribution was as follow 120 males (35.2%) and 221 females (64.8%).

One hundred and forty three patients (42.0%) had the genotype GG (wild type group) and 198 (58.0%) patients were A carriers; GA (164 patients, 48.1%) or AA (34 patients, 9.9%) (mutant type group). Age was similar in both groups (wild type: 41.3 ± 10.9 years vs mutant group: 42.3 ± 11.7 years: ns). Gender distribution was similar in both groups (males in wild type group: 36.1% vs females: 63.9% and males in mutant type group: 33.9% vs females: 66.1%).

Table 1 shows the distribution of genotypes and allelic percentage in the different Health Areas. The Health Areas of Valladolid and Segovia had a lower percentage of wild type genotype (GG) and G allelic than all the others Health Areas. Burgos Health Area had the highest percentage of wild type genotype (GG) of all the health areas mentioned.

Table 2 shows the differences in anthropometric variables. In patients with GG genotype or so called non-A allele carriers (deltas), BMI (0.9 ± 1.3 kg/m^2; $p < 0.05$), weight (3.3 ± 1.1 kg; $p < 0.05$), fat mass (2.5 ± 1.1 kg; $p < 0.05$), waist to hip ratio (0.02 ± 0.005 cm; $p < 0.05$) and waist circumference (2.8 ± 1.1 cm; $p < 0.05$) were higher than A allele carriers. No differences were detected in fat free mass, waist to hip ratio, systolic and diastolic blood pressures.

Table 3 shows the differences in cardiovascular risk factors. The lipid profile analysis shows that subjects with GG genotype (non-A allele carriers) had higher triglyceride levels than A allele carriers (14.4 ± 3.3 mg/dl; $p < 0.05$). These subjects had lower HDL cholesterol levels than A allele carriers (6.4 ± 2.3 mg/dl; $p < 0.05$). The analysis of glucose homeostasis shows that subjects with GG genotype had higher insulin levels than A allele carriers (3.1 ± 1.0 mg/dl; $p < 0.05$) and higher HOMA-IR than A allele carriers (1.2 ± 0.9 mg/dl; $p < 0.05$). No differences were detected in glucose, total cholesterol, LDL cholesterol and CRP levels.

Table 4 shows nutritional intake during 3 days. No statistical differences were detected in calories, carbohydrate, fat, and protein intakes. Distribution of dietary types of fat was similar in both genotypes.

Table 1
Genotype and allelic distribution in different health areas of Castilla Leon.

Areas	BMI	F/M	Wild type	Mutant type	G	A
Avila ($n = 33$)	37.7 ± 3.1	22/11	42.4%	57.6%	0.73	0.27
Burgos ($n = 37$)	37.2 ± 6.0	24/13	64.9%*	29.7%*	0.60	0.40
Leon ($n = 81$)	37.0 ± 4.9	51/30	49.3%	50.7%	0.72	0.28
Palencia ($n = 12$)	36.4 ± 3.1	7/5	41.7%	58.3%	0.67	0.33
Salamanca ($n = 7$)	35.9 ± 6.0	5/2	42.9%	57.1%	0.57	0.43
Segovia ($n = 31$)	36.9 ± 5.0	21/10	32.3%*	67.7%*	0.62	0.38
Soria ($n = 18$)	36.7 ± 4.8	11/7	50.0%	50.0%	0.69	0.31
Valladolid ($n = 97$)	36.8 ± 5.1	71/26	21.2%*	78.8%*	0.53	0.47
Zamora ($n = 35$)	36.6 ± 4.2	19/16	74.1%	25.9%	0.83	0.17

Wild type: GG and Mutant type: (GA and AA). BMI: body mass index; F/M: female male ratio. (*) $p < 0.05$.

Table 2
Anthropometric variables.

Characteristics	Wild type (GG) ($n = 143$)	Mutant type (GA + AA) ($n = 198$)	*p*
BMI	37.6 ± 4.1	36.8 ± 4.1	0.01*
Weight (kg)	101.3 ± 19.9	98.1 ± 11.2	0.02*
Fat free mass (kg)	56.8 ± 11.2	55.9 ± 10.2	0.32
Fat mass (kg)	42.4 ± 11.1	40.1 ± 9.8	0.02*
WC (cm)	114.3 ± 11.3	111.2 ± 10.7	0.01*
Waist to hip ratio	0.94 ± 0.09	0.92 ± 0.07	0.04*
Systolic BP (mmHg)	129.3 ± 12.1	130.1 ± 11.7	0.35
Diastolic BP (mmHg)	79.8 ± 10.4	80.9 ± 11.3	0.50

Wild type: GG and Mutant type: (GA or AA). BMI: body mass index; BP: blood pressure. No statistical differences. (*) $p < 0.05$.

Table 3
Classical cardiovascular risk factors.

Characteristics	Wild type (GG) ($n = 143$)	Mutant type (GA + AA) ($n = 198$)	*p*
Glucose (mg/dl)	95.1 ± 18.4	99.7 ± 21.3	0.51
Total ch. (mg/dl)	191.4 ± 36.5	197.8 ± 31.4	0.68
LDL-ch. (mg/dl)	118.7 ± 32.5	121.8 ± 33.6	0.51
HDL-ch. (mg/dl)	47.1 ± 12.4	53.5 ± 13.4	0.04*
TG (mg/dl)	130.9 ± 47.1	116.6 ± 33.4	0.03*
Insulin (mUI/L)	17.6 ± 12.1	14.6 ± 11.4	0.01*
HOMA-IR	4.19 ± 2.10	3.10 ± 1.8	0.01*
CRP (mg/dl)	3.5 ± 5.1	3.7 ± 5.4	0.33

Wild type: GG and Mutant type: (GA or AA). Cholesterol. TG: triglycerides; CRP: c reactive protein. HOMA-IR: homeostasis model assessment. (*) $p < 0.05$.

Table 4
Dietary intake.

Characteristics	Wild type (GG) ($n = 143$)	Mutant type (GA + AA) ($n = 198$)	*p*
Energy (kcal/day)	2055.2 ± 755.1	1958.9 ± 742.1	0.61
CH (g/day)	222.2 ± 51.3	198.4 ± 61.5	0.72
Fat (g/day)	89.6 ± 41.7	89.9 ± 40.6	0.51
S-fat (g/day)	25.1 ± 12.0	25.9 ± 13.0	0.44
M-fat(g/day)	39.7 ± 20.9	41.1 ± 18.2	0.49
P-fat (g/day)	9.8 ± 7.0	10.1 ± 7.1	0.61
Protein (g/day)	94.6 ± 30.1	92.1 ± 21.2	0.79
Dietary fiber (g/day)	16.9 ± 6.0	14.9 ± 7.0	0.80
Cholesterol (mg/day)	400.1 ± 178.0	318.3 ± 219.1	0.24

Wild type: GG and Mutant type: (GA or AA). Carbohydrate. S-fat: saturated fat; M-fat: monounsaturated fat; P-fat: polyunsaturated fat. No statistical differences.

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3. Discussion

Our cross sectional study showed a relationship between the rs6923761 *GLP-1 receptor* polymorphism and body weight, fat mass, triglycerides, HDL cholesterol, insulin and HOMA_IR in obese subjects. Other finding of this study is the different prevalence of this polymorphism in a geographic Area of Spain (Castilla y Leon).

Nowadays, GLP-1R system is one of the new pathways to target in the development of treatments to diabetes mellitus type 2 with two different families of drugs (inhibitors of type IV dipeptidyl and GLP1 receptor agonists). The evaluation of the SNPs of GLP1R may be important to the rate onset of cardiovascular risk factors in obese subjects in order to design further interventions in these patients taking to account genetic variant of this receptor [5]. Several GLP-1 R polymorphisms have been evaluated in vitro [7,18], although not studied in a wide range on obesity populations and different geographic areas [9,19]. Some authors [20] have identified major pharmacological differences in the signaling profile modulation of multiple GLP1-R polymorphism, the most frequent substitution is Gly 168 Ser (G → A) rs6923761; In this study [20], an altered insulin secretory response to infused GLP-1 was reported in 88 healthy individuals. By contrast to the referred study with a low prevalence of the mutant allele (A allele = 29%), our present study shows an elevated prevalence of A allele (58%). In another study [19] with obese patients without diabetes mellitus, the prevalence of A allele was 49.3%. Other design [9] with diabetes mellitus naïve patients the prevalence was elevated (52.3%), too. All of these studies were carried out in Caucasian population, but even so, the prevalences were different, as well as geographic location of the studies were different. Our geographic area (Castilla y Leon) is located in the northwest of Spain and it was observed statistical differences in the prevalence of this polymorphism, too. Valladolid and Segovia Health Areas had a higher frequency of A allele than the others. Burgos Health Area had a higher frequency of wild type genotype. These differences could be explained by migrations in this geographic Area, different genetic background of the population or maybe other unknown factors. Thus, these localized differences should be taken into account when addressing a personalized medicine in these obese patients.

Data from our study showed better anthropometric and metabolic parameters in carriers of A allele. Triglycerides, insulin levels and HOMA-IR were lower in subjects with A alelle than non A allele carriers. HDL cholesterol was higher in A allele carriers than in non A allele carriers. Moreover, the presence of A allele was associated with lower body mass index, body weight, fat mass and waist circumference than the absence of A allele. These results in anthropometric parameters and lipid profile are in agreement with previous studies [19]. Moreover, the better levels of insulin and HOMA-IR in A allele carriers is the first time that they were described.

Few studies have evaluated the relationship between SNPs of GLP1-R and these cardiovascular risk factors. Tokuyama et al. [7] studied nine polymorphisms in GLP-1 R and there were no significant differences in body mass index and insulin resistance among these genetic variants. However, rs6923761 was not evaluated in this study. The mechanism by which GLP-1 R variants influence on these variables is unclear. Perhaps, the loss of effect of GLP-1 receptor interacts with insulin sensitivity. It is also possible that this SNP variant may be capturing functional effects of a flanking linked SNP, and variation of this locus may influence lipid and carbohydrate metabolisms.

This loss of effect is likely [20,21] to be chemotype-dependent, when glycine at position 168 is replaced by a serine. Perhaps the GLP-1R signaling pathway is partially disrupted, insulin sensitivity, insulin secretion and glucose effectiveness would be repaired. For example, recently has been described these GLP1R missense variant was associated with a reduced response to gliptin [22] or liraglutide [23] treatments. Further studies are needed to evaluate the molecular basis of our data. In vitro studies [24] have showed that genetic variation in GLP1R is associated with altered gastric emptying in mice. Evidence of genetic variation is that GLP1R shows allelic imbalance in stomach but not in pancreas or hypothalamus, suggesting the existence of a mutation or sequence variant in either tissue-specific regulatory elements or other non-coding regions.

The limitations of our study are that sample size, that was small and the heterogeneity of the sample, related to BMI and age. Secondly, the current association's results cannot be interpreted as causative. Finally, the lack of postprandial results such as oral glucose overload test.

In conclusion, our data showed a relationship of metabolic parameters with the mutant allele (A) of rs6923761 *GLP-1 receptor* gene in obese subjects without diabetes mellitus. Body mass index weight, fat mass, waist circumference, triglycerides, insulin, HOMA-IR and HDL-cholesterol levels were better in carriers of A allele than in non carriers. Allelic frequency of A allele is different according to different geographic areas and this fact must be taking into account in order to develop a personalized medicine to treat cardiovascular risk factors in obese subjects.

Conflict of interest

There is no conflict of interest.

Financial disclosure statement

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