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Clinical Pharmacogenomic of Vildagliptin in Egyptian Patients with Insulin Resistance

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Abstract

Background: Pharmacogenomics is the study of how genes affect a person's response to drugs. Insulin resistance is a pathological state in which a given insulin concentration produces a less-than-expected biological effect.

Aim: This study aimed to investigate the association of rs6923761 variants in GLP-1R gene response to vildagliptin after 6 months' follow-up in Egyptian patients with insulin resistance (IR).

Methods: This study included 70 patients attending the outpatient clinics of the Diabetic Department, National Institute of Diabetes and Endocrinology. Metformin 1000 mg and Vildagliptin 50 mg were added for 6 months. Genotyping of the rs6923761 variant of the GLP-1R gene was performed using the restriction fragment length polymorphism–PCR (RFLP–PCR) method.

Results: HbA1c reduction there was a significant difference among wild (GG), and mutant alleles (GA+AA) groups after 6 months of treatment of metformin 1000 mg and vildagliptin 50 mg ($p < 0.05$) of GLP-IR rs6923761 variant ($P<0.05$) and HbA1c, TC, TC/HDL, LDL/HDL there was significant difference between the three different genotypes GG, GA, AA of GLP-IR rs6923761 variant ($P<0.05$). there was no significant difference in response of glycemic and lipid parameters to vildagliptin 50 mg among the different genotypes of GLP1R rs6923761 variant in 70 IR patient's groups after 6 months ($p > 0.05$). also, there was no significant difference in response of glycemic and lipid parameters to vildagliptin 50 mg among wild (GG) , and mutant alleles (GA+AA) groups after 6 months ($p > 0.05$).

Conclusion: the study results indicate that the effects of variation in GLP-IR (rs6923761) the clinical efficacy of Vildagliptin was important in treating insulin resistance.

Keywords: obesity, GLP1R gene, vildagliptin, insulin resistant

Statements and Declarations

Declaration of interests

The authors declare that they have no conflict of interest with this work.

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Declarations

The authors certify that the work has not been published previously, it is not under consideration for publication elsewhere; it does not duplicate or overlap other published work; and, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. The authors will take public responsibility for the contents

All authors have contributed substantially to the drafting and have approved the final version; and the responsible authorities where the work was carried out had approved the publication.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Introduction:

Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup.

Many drugs that are currently available are "one size fits all," but they don't work the same way for everyone [1] .

Pharmacogenomics is rapidly developing and expanding as a key element of precision medicine, in which the association between individual genetic variabilities and drug disposition and therapeutic responses are investigated [2]

The field of pharmacogenomics is still in its infancy. Its use is currently quite limited, but new approaches are under study in clinical trials. In the future, pharmacogenomics will allow the development of tailored drugs to treat a wide range of health problems, including cardiovascular disease, Alzheimer disease, cancer, HIV/AIDS, and asthma [1].

Insulin resistance is pathological state in which a given concentration of insulin produces a less-than-expected biological effect. The syndromes of insulin resistance make up a broad clinical spectrum, which includes obesity, glucose intolerance, diabetes, and the metabolic syndrome, as well as an extreme insulin-resistant state [3].

This study was aimed to investigate the association of rs6923761 variants in GLP-1R gene response to vildagliptin 50 mg after 6 months' follow up .in Egyptian patients with insulin resistance IR.

Subjects and Methods

This study was carried out at National Institute of Diabetes and Endocrinology, this study included 70 patients from those attending the outpatient clinics Diabetic Department, National Institute of Diabetes and Endocrinology. According to the clinical examination, laboratory findings result, subjects sharing in this study were insulin resistance group: this group included 70 patients with insulin resistance.

Exclusion criteria (Excluded subjects): Patient received insulin injection, patients were treated with insulin injection, patients with history of autoimmune disease, as

diabetes mellitus, patients with history of cancer, patients with insulin resistance (HOMA IR ≤ 2.9), pregnant women and patients with age <18 years OR >65 years.

Inclusion criteria (Included subjects): Patients with insulin resistance (HOMA IR >2.9), patients with diabetes mellitus, prediabetes mellitus, patients were treated with metformin, sitagliptin, vildagliptin, linagliptin, alogliptin, and sitagliptin and patients aged 30-65 years. Vildagliptin in a daily dose 50 mg, was added to the previous treatment with metformin 1000 mg. A written informed consent was obtained from each individual and the protocol was approved by the ethical committee of National Institute of Diabetes and Endocrinology.

All patients and were subjected to the following:

Informed consent was obtained from each participant, demographic, age, gender, onset of DM, duration of disease. Full history taking, complete clinical examination and Laboratory investigation including Anthropometric measurements: Weight (KG), Height (M) and Body mass index (KG/M^2), Systolic blood pressures SBP (mm Hg), diastolic blood pressure DBP (mm Hg) and heart rate pulse (bpm).There are two routine laboratory tests and fasting blood sugar (FBS), and fasting blood insulin, HbA1c, and lipid profile such as total cholesterol (TC), low-density lipoprotein (LDL), high -density lipoprotein (HDL), triglycerides (TG),creatinine, urea, are measured at baseline and followed for 6 months for each patient after entering the study.

Method of genotyping: -

Genomic DNA was isolated from peripheral blood leukocytes by standard salting out method and genotyping for (rs6923761) variations was performed using the restriction fragment length polymorphism–PCR (RFLP–PCR) method. For polymerase chain reaction amplification, the following primers were used:

forward 5′-TCTCTTTCTTGGTCTTGGTATCCCC-3′ and reverse:5′ CAACCTCATATTCTACGGTCAGGGC-3′ A Perkin Elmer Gene Amp 9700 PCR System (Applied Biosystems, Foster city, CA, USA) was used for the amplification. PCR conditions were as follows: an initial denaturation step of 10 min at 95°C followed by 30 cycles of den 95°C for 30 s, annealing at 55°C for 30 s and 72°C for 30 s, and finally extension at 72°C for 10 min.

The PCR products were digested with DdeI restriction endonuclease. The digestion of 398 bp amplicon of rs6923761 (AA) genotype resulted in 235 bp and 163 bp fragments: the (GG) genotype remained 398 bp; while the heterozygous genotype (GA) 163, 235, 398 bp fragments.

Statistical analysis: For the entire study cohort, data were collected for all analyzed parameters and tabulated. Raw data were coded, transformed into coding sheets, managed, and stored into SPSS program (SPSS package version 22 for Windows, Chicago, IL, USA © 2013). Genotypes and alleles frequencies were compared between responder and non-responder groups and by Chi-square test. Fisher's exact test was used if cell expected frequencies were < 5.

Data were grouped into two main categories:

Qualitative categorical variables (Genotypes, alleles, gender): Descriptive statistics including Genotype and allele frequency distributions were used to describe different characteristics.

Quantitative variables (All measured biochemical parameters): Descriptive statistics including mean, standard deviation, standard error "SEM", were used to describe different characteristics. To test the significance of results for the continuous data variables among three different groups, One way ANOVA .and among two different groups, unpaired student t-test. All P-values were two-tailed (Two-sided) and the significance of the results was set at the 5% level of significance (P-value < 0.05 was considered as statistically significant) (Norman and Streiner, 2000).

statistical analysis was applied to the insulin resistance IR patients (№ = 70) who were classified according to their genotypes (GG=37, GA=27, AA=6) and according to wild type (GG=47) and mutants' alleles (GA+AA=33) both at base line and after 6 months. Classification of the patients into Responders (R) and Nonresponders (NR) according to % alterations in glycemic and lipid parameters according to the rule

$$\%\ Alteration = \frac{(paramter\ after\ 6\ months - parameter\ at\ basline)}{paramter\ at\ baseline}\ x\ 100$$

Table (1): Baseline Characteristics Demographic profiles and Anthropometric measures of different genotypes (GG (37), GA(17), AA(6)) of GLP1R rs6923761 variant in 70 IR patients

Variables	GG (37)	GA (27)	AA (6)	P-Value
Gender	Male (9)	Male (10)	Male (1)	0.429^{NS}
	Female (28)	Female (17)	Female (5)	
Age (Year)	52.73 ± 7.07 52.73 ± 1.16	55.59 ± 7.77 55.59 ± 1.51	52.50 ± 9.18 52.50 ± 3.75	0.299 ^{NS}
BMI (kg / m^2)	35.27 ± 6.71 35.27 ± 1.10	33.50 ± 8.50 33.50 ± 1.63	36.63 ± 2.82 36.63 ± 1.15	0.501^{NS}
SBP (mmHg)	140.70 ± 19.18 140.70 ± 3.153	140.93 ± 21.14 140.93 ± 4.10	145.17 ± 17.61 145.17 ± 7.20	0.875^{NS}
DBP (mmHg)	85.03 ± 13.50 85.03 ± 2.21	85.52 ± 12.10 85.52 ± 2.32	87.67 ± 17.58 87.67 ± 7.20	0.903^{NS}
Pulse (bpm)	86.81 ± 13.90 86.81 ± 2.30	86.41 ± 16.10 86.41 ± 3.10	77.50 ± 9.60 77.50 ± 3.91	0.340^{NS}

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

The baseline demographic profiles and anthropometric measures of 70 patients with insulin resistance were measured and compared before vildagliptin 50 mg therapy.

As indicated in Table (1), there was no significant difference in baseline demographic profiles and anthropometric measures among different genotypic groups (GG (37), GA (17), AA (6)) of GLP1R rs6923761 variant in 70 IR patients (p>0.05).

Table (2) Baseline characteristics demographic profiles and anthropometric measures of different genotypes wild type (GG=37) and mutants' alleles (GA+AA=33) of GLP1R rs6923761 variant in 70 IR patients

Variables	GG (37)	(GA +AA) (33)	P-Value
Gender	Male (9)	Male (11)	0.438^{NS}
	Female (28)	Female (22)	
Age (Year)	52.73 ± 7.07 52.73 ± 1.16	55.03 ± 7.97 55.03 ± 1.38	0.205^{NS}
BMI (kg / m2)	35.27 ± 6.71 35.27 ± 1.10	34.06 ± 7.83 34.06 ± 1.36	0.490^{NS}
SBP (mmHg)	140.70 ± 19.18 140.70 ± 3.15	141.70 ± 20.35 141.70 ± 3.54	0.834^{NS}
DBP (mmHg)	85.03 ± 13.46 85.03 ± 2.21	85.91 ± 12.94 85.91 ± 2.25	0.781^{NS}

Pulse (bpm)	**86.81 ± 13.90** **86.81 ± 2.30**	**84.79 ± 15.31** **84.79 ± 2.66**	**0.564^{NS}**

As indicated in Table (2), there was no significant difference in baseline demographic profiles and anthropometric measures among different genotypes wild type (GG=37) and mutants' alleles (GA+AA=33) of GLP1R rs6923761 variant in 70 IR patients. (P>0.05).

Table (3): after 6 months Demographic profiles and Anthropometric measures of of different genotypes (GG (37), GA(17), AA(6)) of GLP1R rs6923761 variant in 70 IR patients

Variables	GG (37)	GA (27)	AA (6)	P-Value
Gender	**Male (9)** **Female (28)**	**Male (10)** **Female (17)**	**Male (1)** **Female (5)**	**0.429^{NS}**
BMI (kg / m^2)	**33.47 ± 4.31** **33.47 ± 0.71**	**33.36 ± 3.66** **33.36 ± 0.70**	**34.55 ± 2.52** **34.55 ± 1.03**	**0.796^{NS}**
SBP (mmHg)	**134.58 ± 14.25** **134.58 ± 2.34**	**135.10 ± 15.33** **135.10 ± 2.95**	**139.61 ± 9.66** **139.61 ± 3.94**	**0.729^{NS}**
DBP (mmHg)	**84.10 ± 11.45** **84.10 ± 1.88**	**87.64 ± 8.85** **87.64 ± 1.70**	**96.23 ± 22.25** **96.23 ± 9.08**	**0.095^{NS}**
Pulse (bpm)	**84.20 ± 11.12** **84.20 ± 1.83**	**82.58 ± 15.44** **82.58 ± 2.97**	**81.56 ± 3.70** **81.56 ± 1.51**	**0.825^{NS}**

After 6 months demographic profiles and anthropometric measures of 70 patients with insulin resistance were measured and compared after vildagliptin 50 mg therapy. As indicated in Table (3), there was no significant difference in demographic profiles and anthropometric measures among three different genotypes groups after 6 months (p > 0.05).

Table (4) after 6 months Demographic profiles and Anthropometric measures of different genotypes wild type (GG=37) and mutants' alleles (GA+AA=33) of GLP1R rs6923761 variant in 70 IR patients

Variables	GG (37)	GA +AA (33)	P-Value
Age (Year)	**52.47 ± 7.07** **52.47 ± 1.16**	**55.03 ± 7.97** **55.03 ± 1.38**	**0.205^{NS}**
BMI (kg / m2)	**33.47 ± 4.31** **33.47 ± 0.70**	**33.58 ± 3.48** **33.58 ± 0.60**	**0.915^{NS}**
SBP (mmHg)	**134.57 ± 14.25** **134.57 ± 2.34**	**135.88 ± 14.44** **135.88 ± 2.51**	**0.706^{NS}**
DBP (mmHg)	**84.99 ± 11.45** **84.99 ± 1.88**	**89.20 ± 12.94** **89.20 ± 2.14**	**0.144^{NS}**
Pulse (bpm)	**84.20 ± 11.12** **84.20 ± 1.82**	**82.40 ± 14.00** **82.40 ± 2.43**	**0.552^{NS}**

As indicated in Table 4, there was no significant difference demographic profiles and anthropometric measures among different genotypes wild type (GG=37) and mutants' alleles (GA+AA=33) of GLP1R rs6923761 variant in 70 insulin resistance patients after 6 months. (p > 0.05)

Table (5): Glycemic and lipid parameters before and after vildagliptin 50 mg in all patients (n=70)

Variables	Baseline	6 months	p-value
BMI (kg / m2)	**34.70 ± 7.23** **34.70 + 0.86**	**33.52 ± 3.91** **33.52 ± 0.46**	**0.120^{NS}**
HbA1c %	**8.99 ± 2.85** **8.99 ± 0.34**	**8.75 ± 2.33** **8.75 ± 0.27**	**0.355^{NS}**
HOMA-IR	**6.60 ± 5.86** **6.60 ± 0.70**	**6.68 ± 4.91** **6.68 ± 0.59**	**0.743^{NS}**
HOMA-B	**99.47 ± 411.67** **99.47 ± 49.56**	**53.97 ± 44.16** **53.97 ± 5.31**	**0.323^{NS}**
TC	**230.61 ± 61.91** **230.61 ± 7.40**	**215.09 ± 32.39** **215.09 ± 3.87**	**0.034^{S}**
TC/HDL	**6.77 ± 4.27**	**5.56 ± 1.51**	**0.020^{S}**

	6.77 ± 0.51	**5.56 ± 0.18**	
LDL/HDL	**4.12 ± 2.19** **4.12 ± 0.26**	**3.37 ± 1.28** **3.37 ± 0.15**	**0.003^{S}**

In table (5), there was no significant difference between all patient before and after vildagliptin 50 mg regarding glycemic and lipid parameters ($p > 0.05$). Except TC, TC/HDL, LDL/HDL there was significant difference between all patients before and after vildagliptin 50 mg treatment regarding glycemic and lipid parameters ($P < 0.05$).

Table (6): glycemic and lipid parameters before and after vildagliptin 50 mg treatment in patients having homozygous mutant alleles AA (n=6).

	Variables	**Baseline**	**6 months**	**p-value**
AA	**BMI (kg / m2)**	**36.63 ± 2.82** **36.63 ± 1.15**	**34.55 ± 2.52** **34.55 ± 1.03**	**0.104^{NS}**
	HbA1c %	**9.60 ± 2.11** **9.60 ± 0.86**	**9.40 ± 1.20** **9.40 ± 0.49**	**0.817^{NS}**
	HOMA-IR	**6.43 ± 1.92** **6.43 ± 0.78**	**7.91 ± 4.09** **7.91 ± 1.67**	**0.393^{NS}**
	HOMA-B	**42.85 ± 20.46** **42.85 ± 8.35**	**47.13 ± 24.33** **47.13 ± 9.93**	**0.618^{NS}**
	TC	**244.50 ± 79.76** **244.50 ± 32.56**	**216.63 ± 16.29** **216.63 ± 6.65**	**0.471^{NS}**
	TC/HDL	**6.51 ± 2.86** **6.51 ± 1.16**	**5.19 ± 0.75** **5.19 ± 0.30**	**0.386^{NS}**
	LDL/HDL	**4.19 ± 2.99** **4.19 ± 1.22**	**3.19 ± 0.54** **3.19 ± 0.22**	**0.477^{NS}**

In table (6), there was no significant difference in patients with IR having mutant alleles AA before and after vildagliptin 50 mg treatment (n =6) regarding glycemic and lipid parameters ($P > 0.05$).

Table (7): glycemic and lipid parameters before and after vildagliptin 50 mg treatment in patients having heterozygous mutant alleles (GA) (n =27)

	Variables	**Baseline**	**6 months**	**p-value**
GA	**BMI (kg / m2)**	**33.49 ± 8.49** **33.49 ± 1.63**	**33.36 ± 3.66** **33.36 ± 0.70**	**0.930^{NS}**
	HbA1c %	**8.53 ± 2.64** **8.53 ± 0.50**	**8.93 ± 2.12** **8.93 ± 0.40**	**0.363^{NS}**
	HOMA-IR	**5.61 ± 4.22** **5.61 ± 0.81**	**7.88 ± 5.63** **7.88 ± 1.08**	**0.054^{NS}**
	HOMA-B	**54.18 ± 38.57** **54.18 ± 7.42**	**54.45 ± 31.55** **54.45 ± 6.07**	**0.973^{NS}**
	TC	**299.48 ± 66.88** **299.48 ± 12.87**	**227.47 ± 32.69** **227.47 ± 6.29**	**0.859^{NS}**
	TC/HDL	**6.35 ± 2.71** **6.35 ± 0.52**	**6.14 ± 1.75** **6.14 ± 0.33**	**0.653^{NS}**
	LDL/HDL	**4.24 ± 2.40** **4.24 ± 0.46**	**3.75 ± 1.47** **3.75 ± 0.28**	**0.212^{NS}**

In table (7), there was no significant difference in patients with IR having heterozygous mutant alleles GA before and after vildagliptin 50 mg treatment (n =27) regarding glycemic and lipid parameters (P > 0.05).

Table (8): glycemic and lipid parameters before and after vildagliptin 50 mg treatment in wild type of patients GG (n=37)

	Variables	Baseline	6 months	p-value
GG	BMI (kg / m2)	35.27 ± 6.70 35.27 ± 1.10	33.47 ± 4.31 33.47 ± 0.70	0.052^{NS}
	HbA1c %	9.24 ± 3.10 9.24 ± 0.51	8.51 ± 2.60 8.51 ± 0.41	0.048^{S}
	HOMA-IR	7.36 ± 7.18 7.36 ± 1.19	5.91 ± 4.63 5.91 ± 0.72	0.226^{NS}
	HOMA-B	142.88 ± 569.42 142.88 ± 94.87	54.75 ± 54.37 54.75 ± 9.06	0.320^{NS}
	TC	229.19 ± 56.53 229.19 ± 9.29	205.84 ± 31.60 205.84 ± 5.19	0.015^{S}
	TC/HDL	7.11± 5.32 7.11 ± 0.87	5.20 ± 1.28 5.20 ± 0.21	0.032^{S}
	LDL/HDL	4.02 ± 1.94 4.02 ± 0.31	3.12 ± 1.16 3.12 ± 0.19	0.007^{S}

In table (8), there was no significant difference in patients with IR having wild type (GG), before and after vildagliptin treatment (n =37) regarding glycemic and lipid parameters (P > 0.05) except HbA1c %, TC, TC/HDL, LDL/HDL (P< 0.05) there was significant difference in patients with IR having wild Type GG.

Table (9): glycemic and lipid parameters before and after vildagliptin 50 mg in IR patients having mutant alleles (GA+AA) (n=33)

	Variables	Baseline	6 months	p-value
(GA+AA)	BMI (kg / m2)	34.06 ± 7.83 34.06 ± 1.36	33.58 ± 3.48 33.58 ± 0.60	0.697^{NS}
	HbA1c %	8.72 ± 2.55 8.72 ± 0.44	9.01 ± 1.98 9.01 ± 0.34	0.446^{NS}
	HOMA-IR	5.76 ± 3.89 5.76 ± 0.67	7.89 ± 5.33 7.89 ± 0.92	0.034^{NS}
	HOMA-B	52.12 ± 35.97 52.12 ± 6.26	53.12 ± 30.16 53.12 ± 5.25	0.882^{NS}
	TC	232.21 ± 68.29 232.21 ± 11.88	225.47 ± 30.46 225.47 ± 5.30	0.551^{NS}
	TC/HDL	6.38 ± 2.69 6.38 ± 0.47	5.97 ± 1.65 5.97 ± 0.28	0.369^{NS}
	LDL/HDL	4.23 ± 2.46 4.23 ± 0.42	3.65 ± 1.36 3.65 ± 0.23	0.138^{NS}

In table (5), there was no significant difference in patients with IR having mutant alleles (GA+AA) before and after vildagliptin treatment (n =33) regarding glycemic and lipid parameters (P>0.0.5).

Table (10) Response of glycemic and lipid parameters to vildagliptin 50 mg treatment of different genotypes (GG (37), GA (27), AA (6)) of GLP1R rs6923761 variant in 70 IR patients

Parameter		GG	GA	AA	Total	P-value
response of BMI to vildagliptin 50 mg	responders	26	16	5	47	0.441^{ns}
	Non-responders	11	11	1	23	
response of HbA1c to vildagliptin 50 mg	responders	22	11	4	37	0.260^{ns}

	Non-responders	**15**	**16**	**2**	**33**	
response of HOMA-IR vildagliptin 50 mg	**responders**	**19**	**11**	**2**	**32**	**0.573^{ns}**
	Non-responders	**18**	**16**	**4**	**38**	
response of HOMA-B to vildagliptin 50 mg	**responders**	**15**	**13**	**2**	**30**	**0.736^{ns}**
	Non-responders	**22**	**14**	**4**	**40**	
response of TC to vildagliptin 50 mg	**responders**	**27**	**16**	**3**	**46**	**0.364^{ns}**
	Non-responders	**10**	**11**	**3**	**24**	
response TC/HDL to vildagliptin 50 mg	**responders**	**29**	**17**	**3**	**49**	**0.221^{ns}**
	Non-responders	**8**	**10**	**3**	**21**	
response LDL/HDL to vildagliptin 50 mg	**responders**	**27**	**17**	**3**	**47**	**0.453^{ns}**
	Non-responders	**10**	**10**	**3**	**23**	

In table (10) there was no significant difference in response of glycemic and lipid parameters to vildagliptin 50 mg among there different genotypes of GLP1R rs6923761 variant in 70 IR patient's groups after 6 months ($p > 0.05$).

Table (11) Response of glycemic and lipid parameters to vildagliptin 50 mg treatment among IR patients having mutant alleles (GA+AA) (n=33) and wild types (GG)(n=37).

		GG	GA+AA	Total	P-value
response of BMI to vildagliptin 50 mg	**responders**	**26**	**21**	**47**	**0.616^{ns}**
	Non-responders	**11**	**12**	**23**	
response of HbA1c to vildagliptin 50 mg	**responders**	**22**	**15**	**37**	**0.338^{ns}**
	Non-responders	**15**	**18**	**33**	
response of HOMA-IR to vildagliptin 50 mg	**responders**	**19**	**13**	**32**	**0.346^{ns}**
	Non-responders	**18**	**20**	**38**	
response of HOMA-B to vildagliptin 50 mg	**responders**	**15**	**15**	**30**	**0.810^{ns}**
	Non-responders	**22**	**18**	**40**	
response of TC to to vildagliptin 50 mg	**responders**	**27**	**19**	**46**	**0.212^{ns}**
	Non-responders	**10**	**14**	**24**	
response of TC / HDL to vildagliptin 50 mg	**responders**	**29**	**20**	**49**	**0.124^{ns}**
	Non-responders	**8**	**13**	**21**	
response of LDL/HDL to vildagliptin 50 mg	**responders**	**27**	**20**	**47**	**0.315^{ns}**
	Non-responders	**10**	**13**	**23**	

In table (11) there was no significant difference in response of glycemic and lipid parameters to vildagliptin 50 mg among wild (GG) , and mutant alleles (GA+AA) groups after 6 months ($p > 0.05$) .

Discussion

Pharmacogenomics investigates the influence of genes on an individual's reaction to medications. Pharmacogenomics is an emerging discipline that integrates pharmacology and genomics to provide personalized treatments and dosages based on an individual's genetic characteristics, ensuring their efficacy and safety [4].

The aim of the study was to investigate the association GLP1R rs6923761 polymorphisms and their influence on vildagliptin efficacy in Egyptian Insulin resistance patients. And The objective of this study was to investigate the correlation between genetic mutation and polymorphism of the GLP1R gene with the effectiveness of vildagliptin which used to treat insulin resistance (IR).

In our study, there was no significant difference in baseline demographic profiles and anthropometric measures among different genotypic groups (GG (37), GA (17), AA (6)) of GLP1R rs6923761 variant in 70 IR patients (p>0.05), and there was no significant difference in baseline demographic profiles and anthropometric measures among different genotypes wild type (GG=37) and mutants' alleles (GA+AA=33) of GLP1R rs6923761 variant in 70 IR patients. (P >0.05). [5] investigated whether this same variation in GLP1R could affect T2DM patients' responses to DPP-4 inhibitors. They showed the allele and genotype distributions of rs3765467 in the study population. G was the major allele, whereas A was the minor allele in this group. The genotype distribution did not deviated from Hardy–Weinberg equilibrium (P=0.939). Clinical characteristics of the study participants at baseline. The mean duration of diabetes was 9.3 years, and the HbA1c level was ~8.2%. After 24 weeks of DPP-4 inhibitor add-on treatment, fasting blood glucose levels and HbA1c values significantly decreased (from 155.5±44.8mg/dL to 133.7±34.7, P< 0.001 for HbA1c). In addition, total cholesterol and triglyceride levels also decreased significantly.

In our study, there was no significant difference in demographic profiles and anthropometric measures among three different genotypes groups after 6 months (p > 0.05), and there was no significant difference demographic profiles and anthropometric measures among different genotypes wild type (GG=37) and mutants' alleles (GA+AA=33) of GLP1R rs6923761 variant in 70 insulin resistance patients after 6 months. (p > 0.05).

A more recent study as by [6] that investigated two functional GLP1R SNPs, namely rs6923761 and rs1042044 in 51 participants from a more extensive study that consented to genotyping, observed no significant effect of these SNPs on gastric emptying, plasma glucose, and GLP-1 concentrations after enteral infusion of dextrose.

In our study, there was no significant difference in patients with IR having mutant alleles AA before and after vildagliptin 50 mg treatment (n =6) regarding glycemic and lipid parameters (P > 0.05), and there was no significant difference in patients with IR having heterozygous mutant alleles GA before and after vildagliptin 50 mg treatment (n =27) regarding glycemic and lipid parameters (P > 0.05),also there was no significant difference in patients with IR having wild type (GG), before and after vildagliptin treatment (n =37) regarding glycemic and lipid parameters (P > 0.05) except HbA1c %, TC, TC/HDL, LDL/HDL (P< 0.05) there was significant difference in patients with IR having wild Type GG, but there was no significant difference in patients with IR having mutant alleles (GA+AA) before and after vildagliptin treatment (n =33) regarding glycemic and lipid parameters (P>0.0.5).Similar observations were reported in a study that evaluated the combined effects of GLP1R rs6923761 polymorphism on weight loss and anthropometric and metabolic parameters associated with cardiovascular risk factors in 391 obese patients randomized to 3 months intervention with hypocaloric diets with either high monounsaturated fat or high polyunsaturated fat content. Despite better anthropometric parameters in carriers of polymorphic rs6923761 A allele than non-carriers, no weight loss associations were observed in any dietary interventions [7]. there was no significant difference in response of glycemic and lipid parameters to vildagliptin 50 mg among there different genotypes of GLP1R rs6923761 variant in 70 IR patients groups after 6 months (p > 0.05) and) there was no significant difference in response of glycemic and lipid parameters to vildagliptin 50 mg among wild (GG) , and mutant alleles (GA+AA) groups after 6 months (p > 0.05) . found a significant SNP-SNP interaction between SLC47A1 rs2289669 and

SLC22A1 rs594709, which affected the improvement of insulin resistance and blood lipid induced by metformin therapy. Among SLC22A1 rs594709 AA genotypes, patients with SLC47A1 rs2289669 AA genotype showed significantly higher decrease in FBG (p = 0.015), PINS (p = 0.041), and HOMA-IR (p = 0.014) than GA or GG genotypes (Table 4), while, among SLC22A1 rs594709 G allele carriers, patients with SLC47A1 rs2289669 AA genotype showed a greater decrease in TChol (p = 0.013) than GA or GG genotypes [8]

References

[1] 1. G. H. R. 2. https://ghr.nlm.nih.gov/primer/genomicresearch/pharmacogenomics, 2019. . [Online]. Available: https://ghr.nlm.nih.gov/primer/genomicresearch/pharmacogenomics.

[2] C. A. R.-G. a. J. O.-R. Gutierrez-Rodelo, "[Molecular Mechanisms of Insulin Resistance," *An Update.*, pp. (0016-3813)., ..

[3] S. T. Olatunbosun, "Endocrinology Service, SAMMC/59th Medical Wing and Uniformed Services University of the Health Sciences, F Edward Hebert School of Medicine.," 2019.

[4] H. W. G. A. Omar G, "Association among insulin receptor substrate1 genetic polymorphism, sulfonylurea therapeutic efficacy, and insulin resistance in patients with type 2 diabetes mellitus," *Journal of Medicine in Scientific Research,*, Vols. 4(3),, p. 196, 2021.

[5] P. H. K. O. C. E. W. H. L. Y. Han E, "genetic variant in GLP1R is associated with response to DPP-4 inhibitors in patients with type 2 diabetes.," *Medicine.*, p. 95: e5155. 10.1097/MD.0000000000005155., 2016.

[6] C. P. L. M. V. A. C. M. D. A. Anderson B, "Association between allelic variants in the glucagon-like peptide 1 and cholecystokinin receptor genes with gastric emptying and glucose tolerance.," *Neurogastroenterol. Motil,* no. e13724. doi: 10.1111/nmo.13724., p. 32:, 2020.

[7] D. M. C. M. F. Z. A. C. M. G. P. Sathananthan A, "Common genetic variation in GLP1R and insulin secretion in response to exogenous GLP-1 in nondiabetic subjects : A pilot study.," *Diabetes Care.* , vol. d, p. 33:2074–2076, 2010.

[8] G. Y. L. X. Y. J. Z. W. Q. X. Xiao D, "The Impacts of SLC22A1 rs594709 and SLC47A1 rs2289669 Polymorphisms on Metformin Therapeutic Efficacy in Chinese Type 2 Diabetes Patients.," *International Journal of Endocrinology,* vol. 10.1155/201, pp. 1-7., 2016.