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ORIGINAL

The Effects of (rs3765467) polymorphism in the gene encoding GLPR1 on Serum GLP1 Level and Response to Sitagliptin in Combination with Metformin Therapy in Iraqi Type 2 Diabetics Patients

Efectos del polimorfismo (rs3765467) en el gen que codifica GLPR1 sobre el nivel sérico de GLP1 y la respuesta a la sitagliptina en combinación con la terapia con metformina en pacientes iraquíes con diabetes tipo 2

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ABSTRACT

The dipepdityl peptidase-4 (DPP-4) inhibitors, which prevent incretin degradation, have become popular oral hypoglycemic agents for type 2 diabetes. Despite the wide use of DPP-4 inhibitors, little is known of clinical and pharmacogenomics factors that specifically associated with DPP-4 inhibitor treatment response. Meanwhile, a genetics studies identify important factors involved in the progression of diabetes disease, and identify individuals at risk of developing T2DM. Purpose of present study is to assess the possible association of (rs3765467) polymorphism in the gene encoding GLP1R with serum level of GLP1 and glycemic response for the treatment with sitagliptin in combination with metformin in Iraqi diabetic patients. The results indicated that SNP (rs3765467) was not detected in our study population of 90 individuals. However, Sanger sequencing had successfully identified three SNPs for the study population, including rs3765466, rs910163& (rs910162), located within the same region of the target SNP, rs3765467, in the gene encoding GLP1R. Furthermore, these SNPs (rs3765466), (rs910163) & (rs910162) show no significant effect on the response to the treatment based on HbAIc level (patients with HbA1c of less than or equal to 7,0 % are classified as clinical responders, while those with HbA1c greater than 7,0 % are classified as non-responders), but these SNPs significantly affect the serum GLP1 level. Additionally, (rs910163) & (rs910162) genotypes were significantly associated with serum creatinine levels, suggesting a potential role of the (rs910163) & (rs910162) variant in renal function regulation.

Keywords: Gene Polymorphism; GLP1R; GLP 1; DPP 4 Inhibitor; Sitagliptin; SNP.

RESUMEN

Los inhibidores de la dipeptidasa-4 (DPP-4), que previenen la degradación de las incretinas, se han vuelto agentes hipoglucemiantes orales populares para la diabetes tipo 2. A pesar del amplio uso de los inhibidores de la DPP-4, se sabe poco de los factores clínicos y farmacogenómicos que se asocian específicamente con la respuesta al tratamiento con inhibidores de la DPP-4. Mientras tanto, estudios genéticos identifican factores importantes involucrados en la progresión de la enfermedad diabética e identifican individuos en riesgo de desarrollar DMT2. El propósito del presente estudio es evaluar la posible asociación del polimorfismo (rs3765467) en el gen que codifica GLP1R con el nivel sérico de GLP1 y la respuesta glucémica para el

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tratamiento con sitagliptina en combinación con metformina en pacientes diabéticos iraquíes. Los resultados indicaron que no se detectó SNP (rs3765467) en nuestra población de estudio de 90 individuos. Sin embargo, la secuenciación de Sanger identificó con éxito tres SNP para la población de estudio, incluyendo rs3765466, rs910163 y (rs910162), ubicados en la misma región del SNP diana, rs3765467, en el gen que codifica el receptor GLP1. Además, estos SNP (rs3765466), (rs910163) y (rs910162) no muestran un efecto significativo en la respuesta al tratamiento según el nivel de HbA1c (los pacientes con una HbA1c menor o igual al 7,0 % se clasifican como respondedores clínicos, mientras que aquellos con una HbA1c mayor del 7,0 % se clasifican como no respondedores), pero estos SNP afectan significativamente el nivel sérico de GLP1. Además, los genotipos (rs910163) y (rs910162) se asociaron significativamente con los niveles de creatinina sérica, lo que sugiere un papel potencial de la variante (rs910163) y (rs910162) en la regulación de la función renal.

Palabras clave: Polimorfismo Genético; GLP1R; GLP 1; Inhibidor de DPP 4; Sitagliptina; SNP.

INTRODUCTION

It is worth mentioning that Type 2 diabetes (T2DM) accounts for around 90 % of all diabetes cases; it mainly settles because of the body's ineffective use of insulin and inability of pancreatic ß cells to compensate for the enhanced insulin demand resulting in uncontrolled glucose homeostasis.[1] "Over time, poor glycemic control affects several body districts, especially blood vessels and nerves, fostering the development and progression of neuropathies, micro and macrovascular complications, and premature death.[2] The primary goal of T2DM treatment is to prevent or delay complications via strict management of blood glucose and cardiovascular risk factors, as well as self-care activities.[3]

However, many patients with T2DM experience initial success with anti-hyperglycemic drugs, only to become resistant to monotherapy over time, thus necessitating either an ancillary anti-diabetic agent or a transition to insulin in order to restore acceptable glycemic control. Approximately 40 % of the individuals being treated for T2DM fail to reach the desired glycosylated hemoglobin (HbA1c) target of <7 %."[4]

However, "many patients, particularly those with higher baseline glycated haemoglobin (HbA1c) values, may not achieve their glycaemic goals on metformin monotherapy despite titration to maximally tolerated doses, and therefore require additional medication.[5] Sitagliptin, the first of the DPP-4 inhibitors approved in the United States, has been used as an adjunct to diet and exercise in monotherapy and in combination regimens with other oral anti-diabetic drugs.[6] All recent clinical trials hint to the benefit of the early use of sitagliptin, alone or in combination, of any antidiabetic medication. More specifically, GLp-1 or DDP4 inhibitors, have their maximum effect observed when the diabetic process is in its early manifestations."[7]

Individual response to glucose-lowering therapies in type 2 diabetes varies greatly. A number of factors contribute to interindividual differences in antidiabetic drug responses, including age, sex, disease, drug and food interactions, co-morbidity, and genetic factors. Several clinical markers of the glycemic response to DPP4 inhibitors have been identified.[8]

Interindividual variability in therapeutic response is partly due to genetic heterogeneity, and pharmacogenomics is the discipline that investigates how our entire genome influences individual responses to drugs, and more specifically, pharmacogenetics focuses on genetic variation at a population level, and how these variants can affect therapeutic outcomes and incidence of adverse effects.[9] Pharmacogenetics, therefore, is a key component of the translational medicine effort.

Some studies have reported on associations between specific genetic variations and glycemic responses obtained with antidiabetic medications. Pharmacogenetic studies with more common antidiabetic drugs such as metformin and sulphonylureas have already identified potentially clinically relevant genetic modulators of their efficacy and safety.[10,11]

"Pharmacogenetic effects of DPP4 inhibitors have been much less studied. However, DPP-4 inhibitors, to which responses by T2DM patients vary, the genetic factors are not fully understood. Dipeptidyl peptidase 4 (DPP-4) inhibitors are a class of oral hypoglycemic drugs approved by the FDA in 2006. Mechanistically, DPP-4 inhibitors increase incretin levels such as the levels of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptides (GIP). GLP-1 and GIP are gut hormones secreted from L and K cells in the intestine in response to food intake.[12] Both hormones are DPP-4 target proteins and are rapidly degraded and inactivated by proteolysis. Therefore, DPP-4 inhibitors, which can slow enzymatic cleavage that prevents the degradation of active incretins (GLP-1 and GIP), are used to enhance incretin-induced glycemic control. They have been proposed as potential therapeutic agents for T2D treatment.[13] A meta-analysis revealed that DPP-4 inhibitors decrease glycated hemoglobin (HbA1c) levels more markedly in Asians than in non-Asians.[14]

Thus, genetic variations among different ethnic groups may alter the metabolism and therapeutic response of DPP-4 inhibitors, as previously demonstrated by pharmacogenomic and pharmacogenetic studies.[15] Accordingly,

the genetic effects of several genes such as DPP4,[16,17] GLP1R,[18,19] and TCF7L2[20] on the therapeutic response of DPP-4 inhibitors in patients with T2DM have been investigated in clinical trial and case-control studies with a candidate gene approach.

GLP1R encodes the receptor for GLP1 hormone expressed on the cell surface of pancreatic ß-cells. Activation of GLP1 receptor upon binding of GLP1 facilitates glucose-stimulated insulin secretion.[21] There are a few gene variants correlated to DPP4 inhibitor treatment. GLP1R variants have been associated with fasting glucose levels[22] and type 2 diabetes.[23] Therefore, we investigated whether this same variation in GLP1R could affect T2DM patients' responses to DPP-4 inhibitors.

METHOD

Study participants

A cross-sectional involve a selected group of patients with type 2 diabetes whom were diagnosed according to the (American Diabetes Association diagnostic criteria) from those attending The Diabetes and Endocrinology Unite/ Baghdad Teaching Hospital - Medical City in Baghdad, between March 15th, 2024 to August 22th, 2024. The research protocol was approved by the College of Pharmacy Scientific and Ethics Committee, University of Baghdad (RECAUBCP3112024) on Jan 30, 2024. Moreover, a written informed consent was obtained from each participant. All participants were interviewed by the researchers and demographic data were obtained from them and recorded on a data collection sheet, including age, gender, the duration of disease & treatment, waist circumference, body weight and height.

Initially, the study enrolled 98 patients with T2DM. However, only 90 (35 male; 55 female) patients who matched the requirement of the study, after excluding eight patients (3 patients due to non-valid samples and 5 patients due to insufficient patient information). The participants would be distributed according to their responses into two groups including (45 patients; 18 male and 27 female) who responded clinically and (45 patients; 17 male and 28 female) who failed to respond to the treatment. The response was assessed based on HbA1c level after 3 months of treatment, but not more than 12 months of continuous treatment with sitagliptin plus metformin. HbA1c value of less than or equal to 7,0 % was considered as good treatment response and HbA1c values of more than 7,0 % was considered as poor treatment response.[24] Consequently, patients with HbA1c of less than or equal to 7,0 % are classified as clinical responders, while those with HbA1c greater than 7,0 % are classified as non-responders.

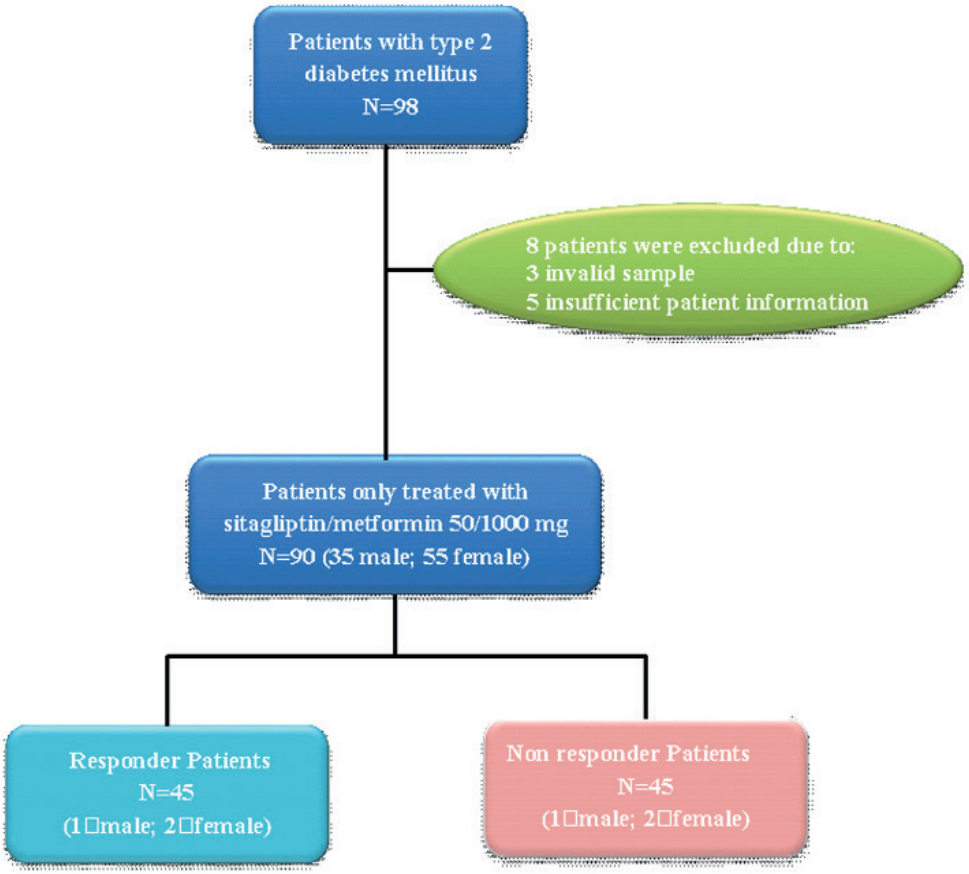

Figure 1. Distribution of Subjects Participated in the Study

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Sample collection and preparation

From each participant, eight ml of venous blood were drawn by venipuncture after at least 8 hours of fasting. Following 30 min of coagulation, 5 ml of the remaining whole blood were transferred to a gel tube. The tube was then centrifuged at 1,008 x g for 10 min at room temperature to extract the serum. Some serum was utilized by the laboratory of the medical center (Specialized Centre for Endocrinology and Diabetes, Baghdad, Iraq) to determine (Fasting serum glucose (FSG), lipid profile, urea, creatinine) levels using an enzymatic colorimetric technique on the same day of sample collection. Aliquots of the remaining serum were divided into 0,5 ml eppendorf tubes and kept frozen at (-20ºC) until the time of assay for insulin and GLP1 levels using ELISA kits. One ml of the collected blood was transferred to (EDTA) tube for analysis of HbA1c at the same center. For DNA extraction, one milliliter of blood was collected into an EDTA tube and store at ($^{+}$2- $^{+}$8) until the time of DNA extraction.

DNA extraction

The Promega ReliaPrepTM Blood gDNA Miniprep System for Genomic DNA (Promega Corp., WI, USA) provides a practical approach for purifying DNA from blood samples. Polymerase Chain Reaction (PCR) was used for enzymatic amplification with the Master Taq polymerase enzyme and a hybrid thermal cycler.

Primers

The primers were designed using the Primer 3 plus, V4, and double checked by the University Code of Student Conduct (UCSC) programs, and with their reference sequences in the National Center for Biotechnology Information (NCBI) database. They were synthesized and lyophilized by Alpha DNA Ltd. (Canada).

Table 1. The Study's Designed Primers

Primer	Sequence (5'→3' direction)	Primer size bp	Product size bp	Ta °C
GLP1R (SNP Genotyping) rs37655467		3		
Variable 2	4	2	577	58
Forward	GCGTATATGTCAGGGGAGGA	20		
Reverse	GGGGATACCAAGACCAAGAA	20		

Note: bp: base pair; Ta: annealing temperature.

Preparing the Primers

For each assay at this study the required primer as shown in table 2 were prepared as follow: after dissolving the lyophilized sample in nuclease-free water according to the manufacturer's instructions, a stock solution with a concentration of 100 µM was prepared and stored at (-20°C). Diluting 10 µL of the primer stock solution in 90 µL of nuclease-free water yielded a working solution with a concentration of 10 µM, which was maintained at (-20°C) until use.

Primer Optimization and Polymerase Chain Reaction (PCR) Amplifications

To examine the optimum annealing temperature of primer, the DNA template was amplified with the same primer pair (Forward) (Reverse), at annealing temperatures of 55, 58, 60, 63, and 65 ºC (182). The best annealing temperature for the primer was 58°C for producing clear and sharp bands in agarose gel; hence, it was used in the current study. Amplifications of PCR were performed with 20µl volumes containing 10µl GoTaq Green Master Mix (2X); 1µl for each primer (10pmol); 6µl nuclease free water and 2µl of template DNA. PCR cycling was performed with PCR Express (Thermal Cycler, BioRad, USA) with the following temperature program: denatured at 94 ºC for 4 min followed by 30 cycles of denaturation at 94 °C for 30 sec; annealing at 55, 58, 60, 63 or 65°C for 30 sec; and extension at 72 °C for 30 sec. A final extension incubation of 7 min at 72 ℃ was included, followed by 10 min incubation at 4 ℃ to stop the reactions.

DNA Sequencing

Sanger sequencing was performed on the amplified PCR fragments using an ABI3730XL automated DNA sequencer (Macrogen Corporation, Korea). Geneious software showed the genotypes after aligning with a reference sequence in the Gene Bank.

Primer Sequence Matching

Detecting primers for GLP1 gene sequencing, and GLP1 gene SNP (rs37655467) genotyping were prepared. The primer sequences were designed in accordance with their reference sequences (rs) in the NCBI (National

Center for Biotechnology Information) database. The genotyping primer sequences were matched by NCBI's bioinformatics programs.

Figure 2. Bioinformatics programs/NCBI was used to match the primers sequences

RESULTS

Figure 2 illustrates the demographic and clinical data of the participants, where the responder's group in the current study were matched with the non-responders' group regarding the gender, age, BMI, serum GLP1, serum urea levels and GFR as there were no significant differences concerning these parameters (P>0,05). Whereas there is a significant difference between two groups in duration of disease & treatment, waist circumference, HbA1c, FBS, HOMA-IR, serum insulin, serum creatinine, serum triglyceride and serum total cholesterol levels mean values.

With respect to the gender, there is no significant difference between two groups (p value 0,8), the responders' group was classified into males (n=17) with percent 37,8 % and females (n=28) with percent 62,2 %. At the same time, the non-responder's group was classified into males (n=18) with percent 40 % and females (n=27) with percent 60 %. Also, there is no variation between the responders and non-responders' groups concerning their age and BMI (p value 0,5 & 0,2 respectively). This indicates both groups are comparable in age and it's consistent with another study that showed the diabetic prevalence in both genders reaches its peak between 40 and 59 years and the prevalence of T2DM in women is higher than in men.[25]

Additionally, with respect to the BMI data was available, which were comparable between the two groups. High BMI has been found as an independent predictor for poor response to DPP4i in 2 Japanese studies[12,13] and could not observe any significant relationship between BMI and DPP4i response in this study. Lim et al. did not report any relationships between them either. One possibility is through insulin resistance, because obesity is closely linked to insulin resistance.[26] Generally the obesity prevalence in Iraqi population is significant and requires serious consideration by health policymakers and public health specialists to plan an effective and preventive provisions to avoid serious health consequences.[27]

With respect to the duration of disease and therapy there is a significant difference between responders and non-responders' group (p value 0,03 and 0,04 respectively), This implies that the treatment response increases as the duration of the disease decreases, while the treatment response increases as the duration of therapy increases.

Additionally, there is significant difference between responders and non-responders' groups (p value 0,03) concerning the waist circumference. The glycemic parameters of included patients, HbA1c, FBS, serum insulin level and HOMA-IR shows there is a significant difference (p value 0,001 for all glycemic the parameters except for serum insulin level p value 0,023) between responders and non-responders' groups. Our results are consistent

with those of other studies that show that markers of higher insulin resistance are consistently associated with reduced glycemic response to DPP4 inhibitor therapy.[28] Also, as in a study that observed T2DM patients are associated with high insulin resistance and may have apparently normal or elevated insulin levels, the higher levels of serum glucose in those patients would lead to even higher insulin levels with the normal function of their ß-cells.[29] The serum GLP1 level had no significant difference between responders and non-responders' group (p value 0,6).

Regarding to the renal function, there is no significant difference in serum urea and GFR between responders and non-responders' group (p value 0,1 and 0,9 respectively), while a serum creatinine shows significant difference between the same groups (p value 0,01). Regarding the results, the serum urea and creatinine levels were higher in the non-responders than in the responders.

With respect to lipid profile there is significant difference in serum triglyceride and total cholesterol levels between responders and non-responders' group (p value 0,01 for both).

Table 2. Demographic data and clinical characteristic parameters of the study

Criterion		Responders(n=45)		Non Responders(n=45)		p-value
		Mean	SD	Mean	SD	
Gender, n(%)	Male	37,8 %	-	18,40 %	-	0,8 ns
	Female	62,2 %	-	27,60 %	-	
Age (years)		56,57	7,64	55,57	8,40	0,5 ns
BMI (kg/m^2)		28,49	4,75	29,85	5,18	0,2 ns
Duration of disease (years)		4,71	3,66	6,37	3,81	0,03*
Duration of treatment (months)		6,98	3,78	5,40	3,55	0,04*
Waist Circumference(cm)		95,17	12,55	100,89	13,42	0,03*
HbA1c		6,08	0,69	9,52	1,52	0,001**
FBS		124,8	21,87	215,55	80,79	0,001**
S. insulin (mIU/ml)		21,41	8,94	28,07	7,19	0,023*
HOMA-IR		6,67	2,05	15,93	5,65	0,001**
S. GLP1 (Pmole/L)		27,01	6,79	26,21	7,06	0,6 ns
Urea mg/dl		37,68	8,86	41,34	10,71	0,1 ns
Creatinine mg/dl		0,69	0,13	0,79	0,25	0,01*
GFR		110,63	12,12	110,67	11,14	0,9 ns
TG mg/dl		160,8	47,55	278,33	90,24	0,01*
TC mg/dl		184,5	41,53	229,91	71,82	0,01*

Note: data were expressed as mean ± SD; Statistical analyses were performed by T-test. SD: standard deviation, BMI: body mass index, FBS: fasting blood sugar, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, GLP1: Glucagon-like peptide-1, GFR: glomerular filtration rate, ns: no significant difference, TG: Triglyceride, TC: Total cholesterol, **significant at the 0,01 level (2-tailed), * significant at the 0,05 level (2-tailed).

GLP1R gene polymorphism rs3765467

The SNP (rs3765467) was not detected in our study population of 90 individuals. Previous research in other populations suggested a potential role of this SNP in great reduction in HbA1c in responders to DPP4 inhibitors for at least 24 weeks in 246 Korean patients with type 2 diabetes.[18] Another study for Korean patients with T2DM carrying (rs3765467) mutant allele A (GA/AA) showed a significantly better hypoglycemic effect to DPP-4 inhibitors than those with genotype GG, indicating that mutant genotype GA/AA could improve the function of GLP-1R mediating insulin secretion, while the major genotype GG might be a risk factor for disease.[30] However, the absence of this SNP in our study may be due to allele frequency differences in our specific population, highlighting the importance of population diversity in genetic research. This finding underscores the need for future studies with larger, diverse samples to verify this SNP's association across different groups.

Sanger sequencing successfully identified several SNPs in the study population, including rs3765466, (rs910163) & (rs910162) located within the same region as the target SNP, rs3765467 as in figure 3 and 4. The presence of these SNPs confirms the reliability of our sequencing methods.

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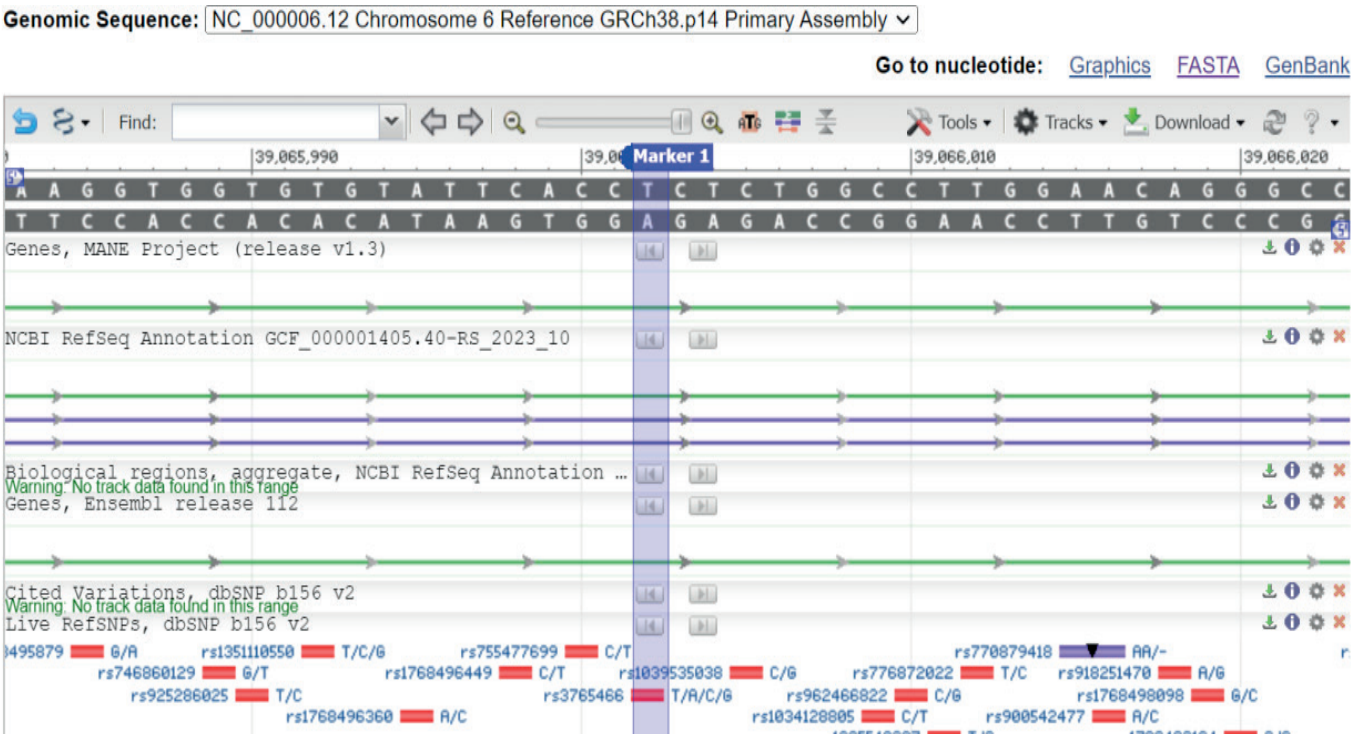

Figure 3. The Geneious program sequence alignment findings for the Homo sapiens GLP1R/promoter fragments (rs3765466) confirmed the compatibility of sample sequences with a reference sequence from the Gene Bank

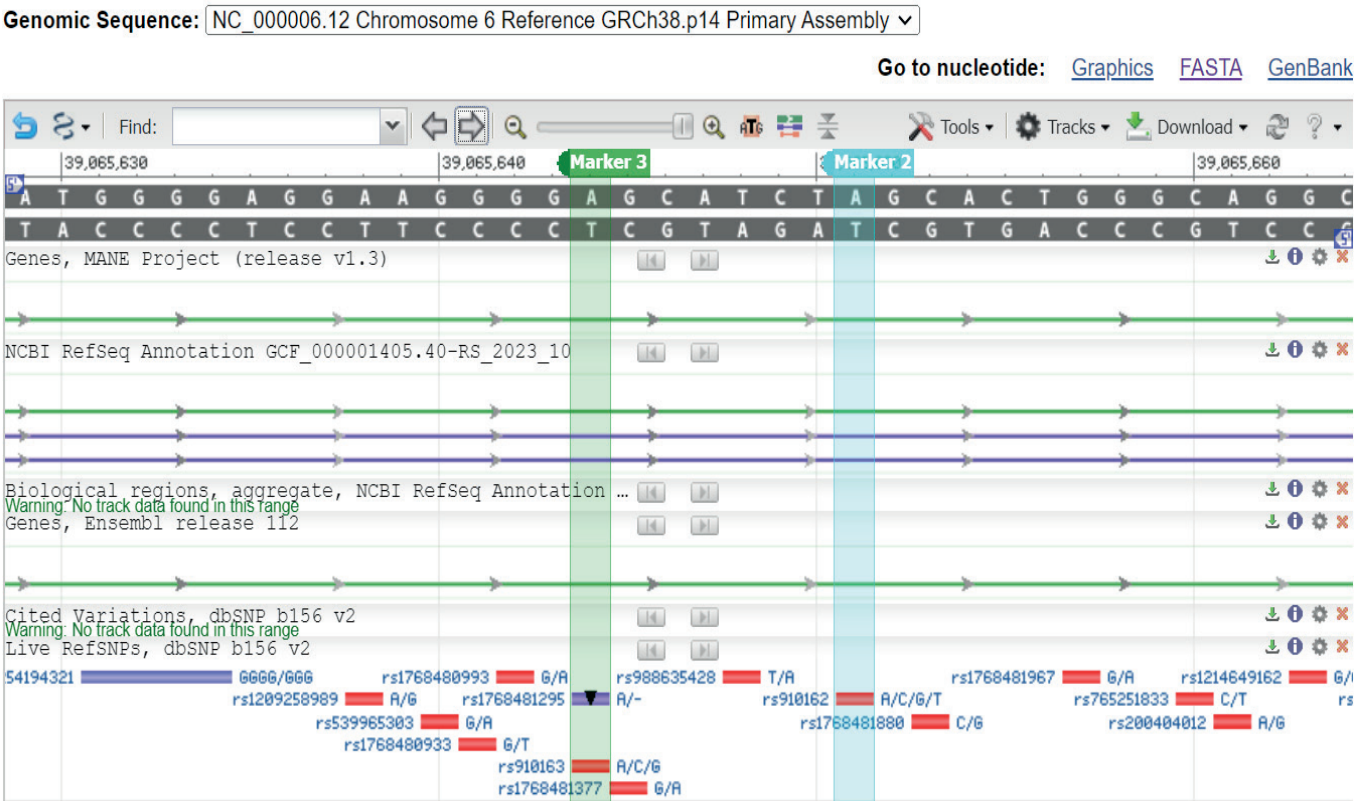

Figure 4. The Geneious program sequence alignment findings for the Homo sapiens GLP1R/promoter fragments (rs910163) & (rs910162) confirmed the compatibility of sample sequences with a reference sequence from the Gene Bank

Prevalence of genotypes and alleles for the responders and non-responders' groups

The genotype frequencies of the patient's analysis, as reported in tables 3, 4 and 5, demonstrate that the wild type genotype and allele have been used as a reference. Table 3 shows the distribution of genotype and allele frequencies analyses for the rs3765466 SNP between responders and non-responders' groups. Out of 45

for each the responders and non-responders' groups, higher proportions of heterozygous (TA) genotypes in both groups which is the most prevalent and present in more than three-quarters of the participants, followed by homozygous mutant (AA) and the lowest one, homozygote (TT). The frequencies of the (TA) and (AA) genotypes did not differ significantly between the groups (p value 0,5 and 0,4) respectively. This implies that these genotypes did not have a risk on the response to treatment than the wild-type TT. Regarding the difference in alleles frequencies the A allele was predominant in the responders and non-responders, the results show no significant difference in T and A alleles of this SNP (table 3).

Table 4 shows the distribution of genotype and allele frequencies analyses for the rs910163 SNP between responders and non-responders' groups. Out of 45 for each the responders and non-responders group, higher proportions of heterozygous (AG) genotypes in both groups which is the most prevalent and present in about two-third of the participants, followed by homozygous mutant (GG) and the lowest one, homozygote (AA). The frequencies of the (AG) and (GG) genotypes did not differ significantly between the groups (p value 0,4 and 0,3) respectively. This implies that these genotypes did not have a higher risk on the response to treatment than the wild-type AA. Regarding the difference in alleles frequencies, the A allele was slightly higher in the non-responders' group while G allele was slightly higher in the responders' group and the results show no significant difference in G and A alleles of this SNP.

In table 5 shows the distribution of genotype and allele frequencies analyses for the (rs910162) SNP between responders and non-responders' groups. Out of 45 for each the responders and non-responders' groups, higher proportions of heterozygous (AT) genotypes in both groups which is the most prevalent. The frequencies of the (AT) and (TT) genotypes did not differ significantly between the groups (p value 0,9 and 0,5) respectively. This implies that these genotypes did not have a risk on the response to treatment than the wild-type TT. Regarding the difference in alleles frequencies the A allele was in the res Regarding the difference in alleles frequencies the A allele was slightly higher in the responders' group while T allele was slightly higher in the non-responders' group, the results show no significant difference in T and A alleles of this SNP (table 5).

Table 3. Genotype and Allele Frequencies Detected by Hardy-Weinberg Equilibrium Law of rs3765466 Gene T/A/C/G Polymorphism SNP

Genotype rs37 65466 T/A	Responders n=45	Non responders n=45	P-value	OR	CI 95 %
TT	1 (2,2 %)	2 (4,4 %)	--	1,00	(Reference)
TA	34 (75,6 %)	35 (77,8 %)	0,5	1,9	0,17 to 22,43
AA	10 (22,2 %)	8 (17,8 %)	0,4	2,5	0,19 to 32,80
Total	45	45	--	--	--
Allele Frequency					
T	36 (40 %)	39 (43,3 %)	--	1,00	(Reference)
A	54 (60 %)	51 (56,7 %)	0,6	1,1	0,63 to 2,08

Note: statistical analyses were performed by T-test, OR: odd ratio, CI 95 %: confidence interval, n: number.

Table 4. Genotype and Allele Frequencies Detected by Hardy-Weinberg Equilibrium Law of rs910163 A/C/G Gene Polymorphism SNP

Genotype rs910163 A/C/G	Responders n=45	Non responders n=45	P-value	OR	CI 95 %
AA	6 (13,3 %)	9 (20 %)	--	1,00	(Reference)
AG	28 (62,2 %)	27 (60 %)	0,4	1,5	0,49 to 4,96
GG	11 (24,5 %)	9 (20 %)	0,3	1,8	0,47 to 7,12
Total	45	45	--	--	--
Allele Frequency					
A	40 (44,4 %)	45 (50 %)	--	1,00	(Reference)
G	50 (55,6 %)	45 (50 %)	0,4	1,2	0,70 to 2,24

Note: statistical analyses were performed by T-test, OR: odd ratio, CI 95 %: confidence interval, n: number.

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Table 5. Number and Percentage Frequencies Of rs910162 A/C/G/T Genotypes and Their Hardy-Weinberg Equilibrium (HWE) in the Responders and Non Responders Groups

Genotype rs910162 A/C/G/T	Responders n=45	Non responders n=45	P-value	OR	CI 95 %
AA	10 (22,2 %)	9 (20 %)	--	1,00	(Reference)
AT	27 (60 %)	25 (55,6 %)	0,9	0,9	0,34 to 2,78
TT	8 (17,8 %)	11 (24,4 %)	0,5	0,6	0,18 to 2,35
Total	45	45	--	--	--
Allele Frequency					
A	47 (52,2 %)	43 (47,8 %)	--	1,00	(Reference)
T	43 (47,8 %)	47 (52,2 %)	0,5	0,8	0,47 to 1,50

Effects of Rs3765466 Genotypes on the Included Patients

Table 6 illustrates significant difference of alleles of rs3765466 genotypes with serum GLP1 level between the responders and non-responders groups (p value 0,01& 0,04 respectively). Additionally, there is no significant difference of alleles of rs3765466 genotypes with serum insulin level between the responders and non-responders groups (p value 0,5 & 0,7 respectively). From these results, the highest mean of serum GLP1 and insulin levels were in the AA allele carriers while the smallest mean of serum GLP1 and insulin levels were in the TT allele carriers in both groups and rs3765466 genotypes affected on serum GLP1 level only but not on the serum insulin level.

In the table 6 shows the effect of alleles of rs3765466 genotypes on all parameters of the total participants (n=90), the results were consistent with a table, in which alleles of rs3765466 genotype only had a significant effect on the serum GLP1 level (p value < 0,001) while other parameters were not affected (p value > 0,05).

Table 6. Comparison of Allele Of rs3765466 Genotypes with Serum GLP1 & Insulin

Groups	rs3765466	n		GLP1	Insulin
Responders (45)	TT	1	Mean	18,50 c	12,24
			SD	8,22	7,82
	TA	34	Mean	25,28 b	21,58
			SD	7,40	9,40
	AA	10	Mean	33,73 a	21,70
			SD	14,09	7,50
		p-value		0,01**	0,5 ns
Non responders (45)	TT	2	Mean	24,33 b	24,04
			SD	8,90	6,91
	TA	35	Mean	29,69 b	26,08
			SD	7,97	18,71
	AA	8	Mean	32,10 a	29,15
			SD	11,18	9,56
		p-value		0,04*	0,7 ns

Note: data were expressed as mean ± SD; Statistical analyses were performed by ANOVA. ANOVA significance test (2-tailed). SD: standard deviation, GLP1: Glucagon-like peptide-1, significant values are bolded. a and b: different letters mean there is significant difference. Means followed by the same letter are not significantly different. n: number, ns: no significant difference. ** Significant at the 0,01 level (2-tailed).*significant at the 0,05 level (2-tailed).

Table 7. Association of Allele of rs3765466 Genotypes with All Parameters

Parameters	rs3765466 T/A/C/G						p-value
	TT (3)		TA (69)		AA (18)		
	Mean	SD	Mean	SD	Mean	SD	
GLP1	22 a	6,63	25 a	7,75	33 c	12,55	<0,001*
Insulin	21	6,91	24,87	15,33	29,79	8,3	0,6
Age	55,67	12,10	56,36	7,59	55,06	9,29	0,8
BMI	28,41	4,42	29,42	5,03	28,34	5,08	0,6
HbA1c	7,67	1,53	7,77	1,98	7,92	2,64	0,9
FBS	163,00	53,73	167,86	72,79	180,28	85,78	0,8
Urea	35,59	10,67	39,56	12,07	39,94	10,43	0,8
Creatinine	0,62	0,15	0,75	0,22	0,76	0,14	0,5
GFR	114,84	8,17	110,94	11,96	108,84	10,67	0,6
TG	251,50	96,71	212,59	100,35	188,33	177,44	0,4
TC	221,78	34,53	204,17	63,19	189,33	64,14	0,5
Gender Male n=35	5		29		1		0,5
Female n=55	13		40		2		

Note: data were expressed as mean ± SD; Statistical analyses were performed by ANOVA. ANOVA significance test (2-tailed). SD: standard deviation, GLP1: Glucagon-like peptide-1, BMI: body mass index, FBS: fasting blood sugar, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, GLP1: Glucagon-like peptide-1, GFR: glomerular filtration rate, n: number, TG: Triglyceride, TC: Total cholesterol, significant values are bolded. a and b: different letters mean there is significant difference. Means followed by the same letter are not significantly different. ** Significant at the 0,01 level (2-tailed).*significant at the 0,05 level (2-tailed).

Effects of alleles of rs910163 genotypes on the included patients

Table 8. Comparison of Allele of rs910163 Genotypes with Serum GLP1 & Insulin

Groups	rs910163	n		GLP1	Insulin
Responders n=45	AA	6	Mean	24,55 b	20,02
			SD	6,86	9,47
	AG	28	Mean	24,73 b	21,52
			SD	7,29	9,70
	GG	11	Mean	34,15 a	21,85
			SD	13,44	7,14
		p-value		0,01**	0,9 ns
Non responders n=45	AA	9	Mean	21,18 b	21,60
			SD	4,93	14,07
	AG	27	Mean	25,88 b	21,66
			SD	8,72	19,48
	GG	9	Mean	32,22 a	23,77
			SD	10,46	9,01
		p-value		0,03*	0,2 ns

Note: data were expressed as mean ± SD; Statistical analyses were performed by ANOVA. ANOVA significance test (2-tailed). SD: standard deviation, GLP1: Glucagon-like peptide-1, significant values are bolded. a and b: different letters mean there is significant difference. Means followed by the same letter are not significantly different. ns: no significant difference. ** Significant at the 0,01 level (2-tailed). *Significant at the 0,05 level (2-tailed).

Table 8 illustrates significant difference of alleles rs910163 genotypes with serum GLP1 level between the responders and non-responders' groups (p value 0,01& 0,03 respectively). Additionally, there is no significant difference of alleles of rs910163 genotypes with serum insulin level between the responders and non-responders' groups (p value 0,5 & 0,7 respectively). From these results, the smallest mean of serum GLP1 levels were in the AA allele while the highest mean of serum GLP1 levels were in the GG allele in both groups and rs910163 genotypes affected on serum GLP1 level only but not on the serum insulin level.

In the table 9 shows the effect of alleles of rs910163 genotypes on all parameters of the total participants (n=90), our analysis revealed a significant association between the rs910163 genotype with serum GLP1 level (p

value < 0,001) and serum creatinine level (p value 0,004) in diabetic patients, individuals with (AA) genotypes exhibited higher serum creatinine levels compared to those with (GG) genotypes which have lower levels. This suggesting that this genetic variant may play a role in influencing renal function in individuals with diabetes, while other parameters were not affected (p value > 0,05).

Table 9. Association of Allele of rs910163 Genotypes with All Parameter

Parameters	rs910163 A/C/G						p-value
	AA (15)		AG (55)		GG (20)		
	Mean	SD	Mean	SD	Mean	SD	
GLP1	22,35	5,80	25,31	7,99	33,28	11,92	<0,001**
Insulin	20,99	12,08	22,04	16,29	26,71	7,87	0,4
Age	57,73	7,57	56,35	7,30	54,10	9,99	0,3
BMI	27,16	6,12	29,64	4,66	29,88	5,01	0,4
HbA1c	8,29	2,35	7,88	1,85	7,63	2,54	0,5
FBS	200,53	112,03	158,87	55,25	178,50	82,96	0,1
Urea	42,96	13,25	38,82	11,60	38,79	10,49	0,4
Creatinine	0,89	0,35	0,75	0,15	0,70	0,13	0,004**
GFR	108,49	13,28	111,20	11,18	110,74	11,71	0,7
TG	252,45	143,76	246,80	81,59	202,53	172,37	0,1
TC	205,60	66,59	204,53	60,55	215,75	67,78	0,7
Gender Male n=35	7		21		7		0,7
Female n=55	8		34		13		

Note: data were expressed as mean ± SD; Statistical analyses were performed by ANOVA. ANOVA significance test (2-tailed). SD: standard deviation, BMI: body mass index, FBS: fasting blood sugar, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, GLP1: Glucagon-like peptide-1, GFR: glomerular filtration rate, n: number, TG: Triglyceride, TC: Total cholesterol, significant values are bolded. a and b: Different letters mean there is significant difference. Means followed by the same letter are not significantly different. ** Significant at the 0,01 level (2-tailed).*significant at the 0,05 level (2-tailed).

Effects of alleles of rs910162 genotypes on the included patients

Table 10. Comparison of Allele Frequencies of Genotypes Rs910162 with GLP1 & Insulin between the Responders and Non-Responders Groups

Groups	rs910162	n		GLP1	Insulin
Responders	AA	10	Mean	36,19 a	22,78
			SD	12,23	6,79
	AT	27	Mean	24,71 b	21,96
			SD	7,60	9,60
	TT	8	Mean	23,31 b	17,80
			SD	6,24	9,02
		p-value		0,002**	0,4 ns
Non responders	AA	9	Mean	32,22 a	31,77
			SD	9,46	9,01
	AT	25	Mean	26,61b	23,78
			SD	8,44	20,04
	TT	11	Mean	20,37b	23,15
			SD	5,61	13,89
		p-value		0,01**	0,3 ns

Note: data were expressed as mean ± SD; Statistical analyses were performed by ANOVA. ANOVA significance test (2-tailed). SD: standard deviation, GLP1: Glucagon-like peptide-1, significant values are bolded. a and b: Different letters mean there is significant difference. Means followed by the same letter are not significantly different. ns: no significant difference. ** Significant at the 0,01 level (2-tailed).*significant at the 0,05 level (2-tailed).

Table 10 illustrates significant difference of alleles rs910162 genotypes with serum GLP1 level between the responders and non-responders' groups (p value 0,002 & 0,01 respectively). Additionally, there is no significant difference of alleles of genotypes rs910162 with serum insulin level between the responders and non-responders groups (p value 0,4 & 0,3 respectively). From these results, the highest mean of serum GLP1 and insulin levels were in the AA allele while the smallest mean of serum GLP1 and insulin levels were in the TT allele in both groups and rs910162 genotypes affected on serum GLP1 level only but not on the serum insulin level.

In the table 10 shows the effect of alleles of rs910162 genotypes on all parameters of the total participants (n=90), the results were consistent with a table 11, in which alleles of rs910162 genotype had a significant effect on the serum GLP1 level (p value < 0,001). Also, the results showed a significant effect on the serum creatinine level (p value < 0,001) while other parameters were not affected (p value > 0,05).

Table 11. Association of Allele of rs910162 Genotypes with All Parameters

		rs910162 A/C/G/T						
		AA (19)		AT (52)		TT (19)		p-value
		Mean	SD	Mean	SD	Mean	SD	
GLP1		34,31	11,30	25,25	8,10	22,34	5,82	<0,001**
Insulin		26,25	7,71	25,95	16,29	21,06	12,37	0,4
Age		53,68	10,08	56,63	6,94	56,95	8,42	0,3
BMI		28,09	5,06	29,80	4,66	28,53	5,77	0,3
HbA1c		7,55	2,57	7,98	1,83	8,29	2,24	0,3
FBS		158,58	83,25	182,47	56,05	189,63	103,14	0,2
Urea		39,61	10,22	38,73	11,36	41,54	13,86	0,6
Creatinine		0,71 b	0,13	0,76 b	0,14	0,86 a	0,34	<0,001**
GFR		108,89	12,01	111,46	10,46	110,19	14,11	0,5
TG		211,00	172,68	231,69	83,61	255,05	134,62	0,2
TC		201,05	65,24	203,90	59,13	222,37	70,57	0,5
Gender	Male n=35	7		20		8		0,9
	Female n=55	12		32		11		

Note: data were expressed as mean ± SD; Statistical analyses were performed by ANOVA. ANOVA significance test (2-tailed). SD: standard deviation, BMI: body mass index, FBS: fasting blood sugar, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, GLP1: Glucagon-like peptide-1, GFR: glomerular filtration rate, n: number, TG: Triglyceride, TC: Total cholesterol, significant values are bolded. a and b: Different letters mean there is significant difference. Means followed by the same letter are not significantly different. ** Significant at the 0,01 level (2-tailed). *Significant at the 0,05 level (2-tailed).

DISCUSSION

Genetic investigation has also been dedicated to evaluate the interindividual variability in the response to oral and injectable glucose-lowering agents, and in recent years, many pharmacogenetic studies of associations between genetic variants and glucose-lowering drug response have been published. To a large extent, these studies were designed to identify subsets of subjects more or less likely to experience therapeutic response to the drug in question or to develop side effects. Indeed, the care of patients with T2DM requires an individualized approach because of the fact that the disease is heterogeneous, alterations in molecular and pathophysiological pathways of glucose homeostasis differ between subjects, and the variable effects of existing therapies make it difficult to predict individual response to glucose-lowering medications.[31] Clearly, an individualized approach is important because of the multitude of clinical features involved in decision-making including age, body weight, disease duration, life expectancy, glycemic control history, risk of hypoglycemia, adverse effects of glucose-lowering medications, presence of complications and comorbid conditions, and psycho-socio-economic factors."[32]

"In the context of personalized or precision medicine, pharmacogenetic information may be useful for patient stratification in order to identify responders and to balance the benefits of glucose-lowering medications with their potential risks.[33] Give the lack pharmacogenetics study on Iraqi population and the new perspective on treating T2DM, it was hope that this study will help pave the road towered customized pharmacological

therapy by providing information about genetic makeup of Iraqi population.

Some genetic variations, particularly single nucleotide polymorphisms (SNPs), can contribute to the development of diabetic complication. Disease susceptibility variants are related to variations in the induction of nucleotide substitution at specific sites in genes.[34] In this study, we conducted a center cross sectional study based on the important role of GLP-1R in glucose homeostasis aimed to explore genetic impact on response to Sitagliptin. GLP-1R is a kind of G protein coupled receptors.[35] When GLP-1 binds to GLP1R, adenylate cyclase (AC) is activated by G protein to increase the intracellular concentration of cAMP. On the one hand, increased cAMP leads to the closure of K+ channels on the cytomembrane, depolarization of cell, opening of voltage-dependent Ca2+ channels, infux of extracellular Ca2+, increase of intracellular Ca2+ concentration, and synthesis and release of insulin finally. On the other hand, the increased cAMP activates protein kinase A (PKA) to phosphorylate related proteins, which further stimulates the transcription and translation of insulin gene finally.[36]

In addition to the aforementioned hypoglycemic effects of GLP-1, there is strong evidence indicating GLP-1 increases insulin sensitivity in peripheral tissues.[37] The higher levels of GLP-1, by either GLP-1RA and/or DPP-4i administration, can induce peripheral insulin sensitivity through several direct or indirect molecular pathways.[38] In the following paragraphs, we discuss the possible molecular mechanisms involved in the GLP-1 dependent insulin sensitivity.

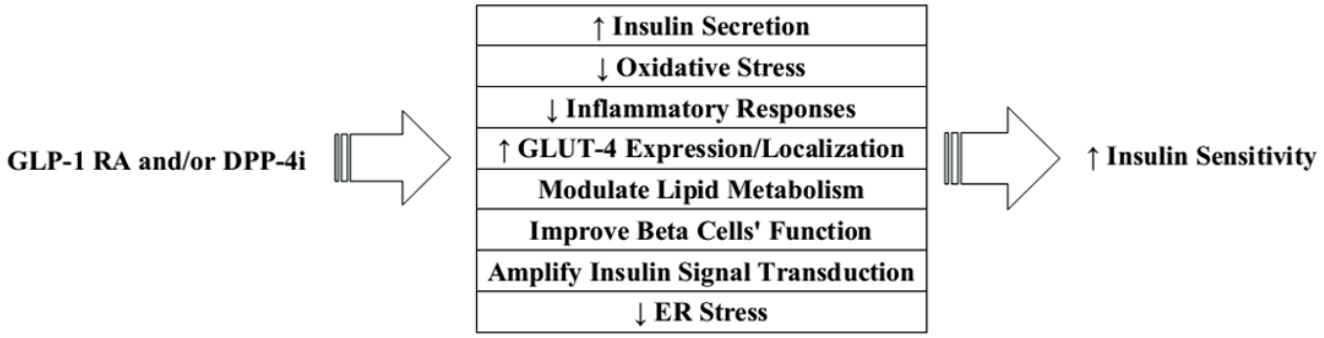

Figure 5. Possible molecular mechanisms involved in the GLP-1 dependent insulin sensitivity

GLP-1 receptors analogues and/or its breakdown enzyme inhibitors are known stimulators for pancreatic beta cells to secrete postprandial insulin in response to higher levels of blood glucose in a concentration-dependent manner. It has suggested that GLP-1 induces insulin secretion through several molecular pathways such as cAMP production, Ca2+ dependent voltage-gated channels, proinsulin granule recruitment and promoting vesicle ducking(21). There is also evidence that DPP-4i can stimulate insulin release.[39] Consequently, GLP-1 based therapies are now routinely used in clinical practice for the treatment of T2DM and obesity.[40] This islet cell stimulating effect of GLP-1 could be one of the therapeutic targets even in some cases of T1DM and/or T2DM with dysfunctional beta-cells.[41]

Since GLP1R is a specific receptor of GLP1, next, our study investigated whether the effects of the SNPs within the GLP1R gene showed to be correlated with the sitagliptin response and GLP1 level. As previously reported, the patients with T2DM suffered a decreased insulin response to GLP-1, thus providing a rationale for the hypothesis that GLP-R deficiency might be involved in the pathogenesis of T2DM.[42,43]

Our study identified three tag SNPs (rs3765466), (rs910163) & (rs910162) of GLP-1R nominally associated with Type 2 DM susceptibility and serum level of GLP1 but don't affect the response to Sitagliptin therapy nor serum insulin level.

Previous studies about these SNPs unavailable except a study in the Chinese population to investigate whether or not the genetic variability in gene GLP-1R affects the risk of cardiovascular disease in type 2 diabetes in the Chinese population included total 611 unrelated Han subjects with type 2 diabetes, 394 individuals with coronary artery disease as cases (CAD) and 217 controls (Non-CAD) were studied.[44]

Regarding the results of genetic polymorphism of GLP1R, this study's findings revealed the presence of rs3765466 (A>T), rs910163 (A>G) and rs910162 (T>A) mutation of GLP1R gene in studied groups. Moreover, the study demonstrated that all genotypes were no significant differences between responsive and non-responsive patients. This implies that these genotypes did not have a risk on the response to Sitagliptin treatment. Inevitably, no published research has looked into how this mutation affects the response of Sitagliptin in type 2 diabetic patients.

The frequencies of these SNPs did not differ significantly between the groups but had a significant correlation with GLP1. The role of the AA of rs3765466 and the GG of rs910163 were supported by a significantly increase serum concentration of GLP1 in both groups, whereas TT of rs910162 were associated by a significantly decrease

serum concentration of GLP1 in both groups.

The significant effect of the (rs910163) & (rs910162) SNPs on serum creatinine levels highlights its potential as a genetic marker for renal dysfunction in diabetic patients. This finding underscores the importance of incorporating genetic profiling into the evaluation of kidney function in diabetes management, as it may provide insights into patient-specific risks and therapeutic strategies.

Among predictors of therapeutic success, two were common to insulin and DPP4 inhibitors: a lower duration of diabetes and a higher BMI. Patients with a shorter duration of diabetes had already been reported as more responsive to DPP4 inhibitors; it can be speculated that the progressive decline of beta-cell functional mass reduces the therapeutic effects of drugs which stimulate insulin secretion, including incretin-based treatments.[45]

Conversely, a higher BMI is not usually reported as a predictor of success in clinical trials; on the contrary, obese patients have sometimes a poorer therapeutic response, as observed in the UK Prospective Diabetes Study.[46] Another retrospective study was performed on a consecutive series of patients with type 2 diabetes in Italy (n = 1,002) failing to at least one oral agent, who had been prescribed either basal insulin or DPP4 inhibitors in the previous 2 years, with a duration of follow-up of at least 6 months. Clinical predictors of success after 6 months from the beginning of second-line treatment were identified in the cohort, among patients receiving a prescription of DPP4 inhibitors produced a therapeutic success in 24,8 % of cases. At multivariate analysis, success was associated with a lower baseline HbA1c and duration of diabetes, and a higher BMI and comorbidity.[47]

Our findings align with previous research concerning the duration of the disease; we observed that the response to treatment declined as the duration of the disease increased. Regarding another predictor of therapeutic success, BMI. Our results are in line with the UK Prospective Diabetes Study[43] that showed BMI of the non-responders were somewhat higher than those of the responders' group, even though our data showed no significant difference in BMI between the two groups.

A study investigated characteristics associated with the efficacy of dipeptidyl peptidase-4 inhibitors (DPP4i) in Korean patients with type 2 diabetes. Its results found that creatinine concentrations were significantly higher in the good response compared to the poor response (1,00 ±0,23 vs 0,91± 0,19 mg/dL, P < 0,001), although they were within the normal range. It also proved that creatinine levels correlated with HbA1c reduction both in the univariate and multivariate analyses.[22] In contrast to our finding that serum creatinine levels were higher in the non-responders' group, they were also in the normal range in the two groups.

According to another study dealing with creatinine levels by Lim et al.[45], response to initial combination of metformin and sitagliptin was not associated with creatinine levels, but Our study is inconsistent with Lim et al., we observed creatinine levels had a significant effect between the groups.

Furthermore, a study reported a significant triglyceride concentration decrease in T2DM patients by 0,2 ± 0,5 mmol/L following sitagliptin treatment, while the change in the total serum cholesterol, LDL- and HDL-cholesterol did not reach the statistical significance.[48]

A study showed that markers of higher insulin resistance are consistently associated with reduced glycemic response to DPP4 inhibitor therapy. In UK-representative cohort 22% of patients were obese with high triglycerides (≥2,3mmol/L) and these patients had both markedly reduced short-term glycemic response and shorter durability of response on DPP4 inhibitor treatment.[49]

In our study, there is statistical significance in both triglyceride and total cholesterol between the responders and non-responders groups and concentrations of triglyceride and total cholesterol were lower in the responders compared to the non-responders group. Our results show that markers of higher insulin resistance are associated with reduced glycemic response to treatment.

A first study on sitagliptin as monotherapy was performed in 743 drug-naïve patients with type 2 diabetes using different doses for treatment duration of 12 weeks. The patients had a mean baseline HbA1c of 7,7 % (61mmol/mol). After 12 weeks of treatment; sitagliptin had reduced HbA1c by 0,8 % (8mmol/mol) with a low risk for hypoglycemia and now eight gains. The DPP-4 inhibitors were also examined as add-on to on-going metformin in subjects with type 2 diabetes in 24–26-week studies with a total number of 3216 subjects. Baseline HbA1c in these studies was 7,9–8,4 % (63–68 mmol/mol). The placebo-adjusted reduction in HbA1c was 0,5–1,1 % (5,11 mmol/mol).[49]

As in previous study our findings show there is a statistical difference in the duration of treatment between the two groups and we noticed as the duration of treatment became longer, the response to treatment increased

The present study had certain limitations which should be mentioned, the present study was not able to accommodate a sufficient amount of time for follow-up between pre- and post-treatment groups of diabetic patients owing to capacity constraints. However, one of the primary limitations of the present study was the small sample size. The limited number of participants may reduce the generalizability of the results, making it difficult to apply the findings to a broader population. The limited financing has restricted the authors' ability to obtain more kits to assess the aforementioned markers. Future studies with larger sample sizes are thus required to validate these findings and enhance their applicability."[50]

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CONCLUSIONS

The study identified three GLP-1R SNPs (rs3765466, rs910163, and rs910162) associated with T2DM susceptibility and GLP1 serum levels but not with Sitagliptin response or insulin levels. While these SNPs had no impact on Sitagliptin response, rs910163 and rs910162 showed significant correlations with serum creatinine, suggesting a potential role in renal dysfunction among diabetic patients. Additionally, our findings emphasized other factors that could affect the response to the treatment, like the duration of the disease and treatment. Moreover, there is a significant difference between the responders and non-responders groups and higher levels of non-responders compare to responders group in waist circumference, HbA1c, FBS, HOMA-IR, serum insulin, serum creatinine, serum triglyceride and serum total cholesterol levels mean values.

BIBLIOGRAPHIC REFERENCES

1. Qin M, Chao L, Liu S. Comparative efficacy and safety of sitagliptin or gliclazide combined with metformin in treatment-naive patients with type 2 diabetes: A randomized study with genetic polymorphism analysis. Medicine (Baltimore). 2025;104(2):e41061. doi: https://doi.org/10.1097/MD.0000000000041061.

2. Fang Y, Song W, Wei L. GLP1R rs3765467 polymorphism is associated with the risk of early-onset type 2 diabetes. J Diabetes Res. 2023;2023:1054192. doi: https://doi.org/10.1155/2023/1054192.

3. Klen J, Dolžan V. GLP-1 receptor agonists in type 2 diabetes management: Pharmacology and genetic factors. Int J Mol Sci. 2022;23(7):3451. doi: https://doi.org/10.3390/ijms23073451.

4. Ma X, Lu R, Gu N, et al. GLP-1R gene polymorphisms and coronary artery disease risk in Chinese Han with type 2 diabetes. J Diabetes Res. 2018;2018:1054192. doi: https://doi.org/10.1155/2018/1054192.

5. de Luis DA, Aller R, Izaola O, et al. rs6923761 variant in GLP-1 receptor and cardiovascular/metabolic parameters in obesity. Nutr Hosp. 2014;29(4):889-893. doi: https://doi.org/10.3305/nh.2014.29.4.7165.

6. de Luis DA, Aller R, Izaola O, et al. GLP1R rs6923761 and metabolic response to hypocaloric diet. J Endocrinol Invest. 2014;37(9):935-939. doi: https://doi.org/10.1007/s40618-014-0116-3.

7. de Luis DA, Aller R, Izaola O, et al. Cardiovascular risk after diets in obese patients with GLP1R rs6923761. J Endocrinol Invest. 2014;37(9):853-859. doi: https://doi.org/10.1007/s40618-014-0116-3.

8. de Luis DA, Pacheco D, Aller R, Izaola O. rs6923761 GLP1R variant and CV risk post-biliopancreatic diversion. Ann Nutr Metab. 2014;65(4):259-263. doi: https://doi.org/10.1159/000365438.

9. Terranegra A, Arcidiacono T, Macrina L, et al. GLP1R and sarcoglycan delta variants and cardiovascular risk in dialysis. Clin Kidney J. 2020;13(4):666-673. doi: https://doi.org/10.1093/ckj/sfz123.

10. Zhang F, Tong Y, Su N, et al. GLP-1 mimetics and weight loss in non-diabetic overweight adults: Meta-analysis. J Diabetes. 2014;7(3):329-339. doi: https://doi.org/10.1111/1753-0407.12238.

11. Vilsbøll T, Christensen M, Junker AE, et al. GLP-1 receptor agonists and weight loss: Meta-analyses. BMJ. 2012;344:d7771. doi: https://doi.org/10.1136/bmj.d7771.

12. Htike ZZ, Zaccardi F, Papamargaritis D, et al. GLP1R agonists in type 2 diabetes: Mixed-treatment analysis. Diabetes Obes Metab. 2017;19(4):524-536. doi: https://doi.org/10.1111/dom.12849.

13. Heo CU, Choi CI. Genetics and pharmacogenomics in type 2 diabetes treatment. Pharmaceutics. 2021;13(5):670. doi: https://doi.org/10.3390/pharmaceutics13050670.

14. Yabe D, Seino Y. Incretin signaling in type 2 diabetes: Genetic insights. Endocr J. 2020;67(6):579-589. doi: https://doi.org/10.1507/endocrj.EJ20-0063.

15. Zhou Y, Han J, Xu J, et al. GLP-1 receptor polymorphisms and antidiabetic drug response: Review. Pharmacogenomics J. 2019;19(6):528-538. doi: https://doi.org/10.1038/s41397-019-0092-7.

16. Zhang Z, Zhang Y, Zhang Y, et al. Cardiovascular risk and GLP-1 receptor agonists: Genetic variability. Cardiovasc Diabetol. 2018;17(1):108. doi: https://doi.org/10.1186/s12933-018-0741-1.

17. Ahrén B, Pacini G. GLP-1 receptor polymorphisms and diabetes therapy outcomes. Trends Endocrinol Metab. 2021;32(4):266-275. doi: https://doi.org/10.1016/j.tem.2021.01.006.

18. Baggio LL, Drucker DJ. Incretin hormone mechanisms and pharmacology. Gastroenterology. 2007;132(6):2131-2157. doi: https://doi.org/10.1053/j.gastro.2007.03.054.

19. Trujillo JM, Nuffer W. GLP-1 receptor agonists: Head-to-head trials in type 2 diabetes. Ther Adv Endocrinol Metab. 2014;5(1):19-28. doi: https://doi.org/10.1177/2042018814524224.

20. Ji G, Zhu L, Zhu S. GLP1R rs3765467/rs10305492 and ß-cell insulin function. DNA Cell Biol. 2020;39(9):1700-1710. doi: https://doi.org/10.1089/dna.2020.5424.

21. Guan Z, Du Y, Li R, et al. GLP-1R polymorphism and response to GLP1R agonists in China. Eur J Clin Pharmacol. 2022;78(5):793-799. doi: https://doi.org/10.1007/s00228-021-03249-z.

22. Li Y, Yang Z, Ren S, et al. GLP-1R polymorphism and dyslipidemia in type 2 diabetes. Gene. 2023;878:147589. doi: https://doi.org/10.1016/j.gene.2023.147589.

23. Qiu X, Huang Y, Cen L, et al. GLP-1R polymorphisms and Parkinson's disease risk. Neurosci Lett. 2020;728:135004. doi: https://doi.org/10.1016/j.neulet.2020.135004.

24. de Luis DA, Diaz Soto G, Izaola O, Romero E. Liraglutide therapy in diabetics and GLP1R RS6923761. J Diabetes Complications. 2015;29(4):595-598. doi: https://doi.org/10.1016/j.jdiacomp.2015.03.005.

25. de Luis DA, Bachiller R, Izaola O, de la Fuente B, Aller R. rs6923761 variant and metabolic syndrome in obesity. Ann Nutr Metab. 2014;65(4):253-258. doi: https://doi.org/10.1159/000365437.

26. Javorsky M, Gotthardova I, Klimcakova L, et al. Missense GLP1R variant and gliptin response. Diabetes Obes Metab. 2016;18(9):941-944. doi: https://doi.org/10.1111/dom.12684.

27. Abd Aliwie AN. A Pragmatic Analysis of Wish Strategies Used by Iraqi EFL Learners. Salud, Ciencia y Tecnología - Serie de Conferencias [Internet]. 2024 Aug. 12 [cited 2024 Sep. 6];3:.1151. Available from: https://conferencias.ageditor.ar/index.php/sctconf/article/view/1151

28. Aliwie, A.N.A., 2024. A Pragmatic Study of Irony in Dickens' 'A Tale of Two Cities'. Forum for Linguistic Studies. 6(6): 147–161. DOI: https://doi.org/10.30564/fls.v6i6.7056

29. Abd Aliwie, A.N., 2025. A Pragmatic Analysis of Persuasive Arguments in the 2011–2020 US Presidential Campaign Speeches. Forum for Linguistic Studies. 7(1): 480–494. DOI: https://doi.org/10.30564/fls.v7i1.7243

30. Abd Aliwie, A. N. (2025). Conversational Silence in Harold Pinter's The Birthday Party: A Pragmatic Perspective. International Journal of Arabic-English Studies. https://doi.org/10.33806/ijaes.v25i2.860

31. Urgeova A, Javorsky M, Klimcakova L, et al. GLP1R variants and response to DPP-4 inhibitors. Pharmacogenomics. 2020;21(5):317-323. doi: https://doi.org/10.2217/pgs-2019-0174.

32. Nunez DJ, Bush MA, Collins DA, et al. GLP1 and sitagliptin pharmacodynamics in type 2 diabetes. PLoS One. 2014;9(4):e92494. doi: https://doi.org/10.1371/journal.pone.0092494.

33. Dorsey-Trevino EG. GLP1R variants and acute response to metformin and glipizide. Harvard Med Sch. 2021. doi: https://nrs.harvard.edu/URN-3:HUL.INSTREPOS:37368019.

34. Aroda VR, Henry RR, Han J, et al. Efficacy and tolerability of GLP-1 receptor agonists in type 2 diabetes. Diabetes Care. 2009;32(1):84-90. doi: https://doi.org/10.2337/dc08-0677.

35. Bergenstal RM, Wysham C, MacConell L, et al. Efficacy of once-weekly GLP-1 receptor agonist therapy. Lancet. 2010;374(9686):39-47. doi: https://doi.org/10.1016/S0140-6736(09)61526-1.

36. Drucker DJ, Sherman SI, Gorelick FS, et al. Incretin-based therapies and safety controversies. Gastroenterology. 2010;139(3):746-759. doi: https://doi.org/10.1053/j.gastro.2010.06.015.

37. Nauck MA, Meier JJ. Incretin hormones: Their role and application. Diabetologia. 2018;61(3):441-445. doi: https://doi.org/10.1007/s00125-017-4506-z.

38. Nauck MA, Quast DR, Wefers J, et al. GLP-1 receptor agonists and SGLT2 inhibitors in type 2 diabetes therapy. Diabetes Metab Syndr Obes. 2021;14:683-698. doi: https://doi.org/10.2147/DMSO.S241136.

39. Lee YS, Jun HS. Anti-diabetic actions of GLP-1 and its analogs. Mol Cells. 2014;37(2):90-98. doi: https://doi.org/10.14348/molcells.2014.2372.

40. Buse JB, Henry RR, Han J, et al. Effects of exenatide on glycemic control and weight. Diabetes Care. 2004;27(11):2628-2635. doi: https://doi.org/10.2337/diacare.27.11.2628.

41. Bailey CJ, Day C. Metformin: Its properties and mechanisms. Diabetes Care. 1989;12(6):557-562. doi: https://doi.org/10.2337/diacare.12.6.557.

42. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes. Diabetes Care. 2012;35(6):1364-1379. doi: https://doi.org/10.2337/dc12-0413.

43. Weng J, Li Y, Xu W, et al. Early insulin initiation improves beta-cell function in newly diagnosed type 2 diabetes. Lancet. 2008;371(9626):1753-1760. doi: https://doi.org/10.1016/S0140-6736(08)60762-X.

44. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control and diabetes complications. Lancet. 1998;352(9131):837-853. doi: https://doi.org/10.1016/S0140-6736(98)07019-6.

45. Alobaidi ZA, Mohammed SI. Olanzapine-induced metabolic syndrome and its association with -759C>T polymorphism of the HTR2C gene in Iraqi schizophrenic patients. Iraqi J Pharm Sci. 2024;33(3):37–46.

46. Mohammed SI, Jasim AL. Genetic polymorphisms associated with diabetic foot ulcer: a review article. Asian J Pharm Pharmacol. 2020;6(4):798–805.

47. Khadim DN, Mohammed SI. Genetic polymorphisms at TNF-alpha receptors associated with some autoimmune diseases and response to anti-TNF biologics: a review. Iraqi J Pharm Sci. 2024;33(4):49–58.

48. Mohammed SI, Zalzala MH, Gorial FI. The effect of TNF-alpha gene polymorphisms at -376 G/A, -806 C/T, and -1031 T/C on the likelihood of becoming a non-responder to etanercept in a sample of Iraqi rheumatoid arthritis patients. Iraqi J Pharm Sci. 2022;31(2):113–28.

49. Alobaidi ZA, Mohammed SI. The association between -697C>G and -997G>A polymorphisms of the HTR2C gene and the metabolic syndrome in Iraqi schizophrenic patients. J Popul Ther Clin Pharmacol. 2023;30(9):271–82. https://doi.org/10.47750/jptcp.2023.30.09.027

50. Al-Jalehawi AK, Mohammed SI. Clinical use of tumor necrosis factor-alpha inhibitors in Iraq: a review of their documented efficacy, safety, and associated genetics. Rev Clin Pharmacol Pharmacokinet Int Ed. 2024;38(3):335–46. https://doi.org/10.61873/SEZR6390

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