Assessment of Factors Affecting Therapeutic Response of the DPP-4 Inhibitor Sitagliptin in A Sample of Iraqi Type 2 Diabetic Patients

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Abstract:

Background: Type 2 diabetes is a complex and diverse disease, and the response to dipeptidyl peptidase-4 inhibitors may exhibit substantial variability between individuals. Several variables may play a role in variances in individual responses to treatment.

Objective: The purpose of the research was to assess the degree to which Iraqi patients with type 2 diabetes responded to sitagliptin and to investigate the factors that contribute to sitagliptin's overall efficacy.

Patients and methods: Eighty patients with type 2 diabetes who were using sitagliptin (100 mg per day) were included in this observational, cross-sectional study. Sociodemographic and patient clinical data were collected. Glycated hemoglobin (HbA1c), lipid profile parameters, and C-reactive protein were measured.

Results: The response rate to sitagliptin was 43.8%. Smokers and hypertensive patients, in addition to those not on diet, had higher HbA1c levels with nearly significant p values than non-smokers, normotensive patients, and those on diet, respectively. Poor response patients had higher levels of total cholesterol and triglycerides.

Conclusions: Possible variables that may have influenced the response to sitagliptin include smoking, hypertension, and an unhealthy diet. Furthermore, elevated levels of triglycerides may serve as an indicator of poor response.

Keywords: Type 2 diabetes, DPP-4 inhibitors, Sitagliptin

تقييم العوامل المؤثرة على الاستجابة العلاجية لمثبط DPP-4 سيتاجليبتين في عينة من مرضى السكري العراقيين من النوع 2

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الخلاصة

خلفية البحث: داء السكري من النوع 2 هو مرض معقد ومتنوع، وقد تظهر الاستجابة لمثبطات DPP-4 تباينا كبيرا بين الأفراد. قد تلعب العديد من المتغيرات دورا في الفروق في الاستجابات الفردية لهذه الادوية.

أهداف البحث: صممت الدراسة لتقييم استجابة المرضى العراقيين المصابين بداء السكري من النوع 2 لسيتاجليبتين وتقييم العوامل التي من الممكن ان تساهم في فعالية سيتاجليبتين.

المرضى وطرق العمل: شملت هذه الدراسة المقطعية القائمة على الملاحظة ثمانين مريضا يعانون من مرض السكري من النوع 2 والذين كانوا يستخدمون سيتاجليبتين (100 ملغ يوميا). تم جمع البيانات الاجتماعية الديموغرافية والسريرية لكل مريض. كما تم قياس التحاليل المختبرية الاتية لكل مريض: السكر التراكمي (HbA1c)، تحليل (C-reactive protein)، إضافة الى تحاليل الدهون الثلاثية والكولستيرول بانواعه.

النتائج: لوحظ ان معدل الاستجابة لدواء سيتاكلبتين هو 43.8%. كما ان المدخنين ومرضى ارتفاع ضغط الدم، بالإضافة إلى أولئك الذين لا يتبعون نظاما غذائيا، كان لديهم مستويات أعلى من HbA1c واستجابة أضعف من غير المدخنين والمرضى الذين لا يعانون من ارتفاع ضغط الدم وأولئك الذين يتبعون نظاما غذائيا، على التوالي. ان المرضى الذين كانت استجابتهم ضعيفة للسيتاغلبتين كان لديهم مستويات اعلى من الكولستيرول الكلي والدهون الثلاثية.

الاستنتاج: تشمل المتغيرات المحتملة التي قد تكون أثرت على الاستجابة لسيتاجليبتين التدخين وارتفاع ضغط الدم واتباع نظام غذائي غير صحي. علاوة على ذلك، قد تكون المستويات المرتفعة من الدهون الثلاثية بمثابة مؤشر على ضعف الاستجابة.

الكلمات المفتاحية: داء السكري من النوع 2، مثبطات DPP-4، سيتاجليبتين

Introduction

Type 2 diabetes (T2D) is a metabolic disorder characterized by persistent hyperglycemia and impaired insulin sensitivity, it develops as a result of an ongoing lack of sufficient β-cell insulin production, which commonly occurs in the context of insulin resistance [1,2]. The prevalence of this chronic illness on a global scale is reaching frightening levels [3,4]. Type 2 diabetes continues to increase in both incidence and prevalence; around 10.7% of Iraqis have been confirmed to have the disease [5,6]. Dietary and lifestyle changes are the first line of treatment for T2D, but many patients eventually require the use of oral hypoglycemic agents (OHAs) to achieve and maintain their blood glucose targets [7].

The inhibition of dipeptidyl peptidase-4 (DPP-4) is an attractive therapeutic strategy for the management of T2D, as it harnesses the physiological phenomenon known as the incretin effect [8]. The Food and Drug Administration (FDA) granted approval for the use of dipeptidyl peptidase 4 inhibitors, commonly referred to as gliptins, as novel oral medications [9]. In 2006, sitagliptin, the first gliptin, received licensing approval for the treatment of diabetes which is a highly selective DPP4 inhibitor given once daily [10]. The DPP-4 inhibitor sitagliptin acts by blocking the DPP-4 enzyme, consequently providing glucagon-like peptide-1 (GLP1) and gastric inhibitory polypeptide with an extended half-life and so allowing GLP1 levels to return to their normal, physiological range in T2D patients [11]. This promotes the pancreas to secrete additional insulin that is glucose-dependent in addition to decreasing unnecessary postprandial glucagon, leading to a lowering of blood glucose levels with no hypoglycemia [12]. Sitagliptin has a low risk of adverse effects, including hypoglycemia, an increase in weight, and the requirement of increased dosing. In addition, with appropriate dosing adjustments, it can be given to patients with chronic kidney disease and to elderly individuals with diabetes [13].

Type 2 diabetes is a complex heterogeneous disease and the response to DPP-4 inhibitors can vary significantly among patients [14]. Several variables play a role in variances in individual responses to diabetes medications, which include age, gender, disease status, potential drug and food interactions, co-existing medical conditions, and genetic influences [15]. There is solid evidence that the extent to which those who have T2D respond to DPP-4 inhibitors varies significantly among T2D patients [16]. Therefore, it is vital to carefully monitor the response of each patient to DPP-4 inhibitors and adjust the treatment plan accordingly to achieve optimal glycemic control and prevent long-term complications [17].

The objective of the current study is to determine the rate of response to sitagliptin and examine the various elements that

impact the overall effectiveness of sitagliptin in Iraqi type 2 diabetic patients.

Patients and Methods

Eighty patients with type 2 diabetes who were using the DPP4-inhibitor sitagliptin were included in this observational, cross-sectional study at the Al Hassan Metabolism, Endocrine, and Diabetes Centre (HMEDC). Patients were informed about the study and given the option to choose not to participate. Oral and written permission was gained once the study's goals were explained in detail and participants' privacy was assured. The research was conducted between the months of February and August of 2022. Patients with T2D who had been on sitagliptin (100 mg per day) for at least six months and were between the ages of 18 and 65 were included. Patients with cancer, kidney disease, endocrine disorders, severe liver disease, and pregnancy was not eligible for the study.

The study gathered sociodemographic and patient clinical data, encompassing variables such as age, gender, body mass index (BMI), dietary habits, lifestyle, smoking, duration of diabetes, and presence of hypertension. Serum from venous blood was used for the estimation of glycated hemoglobin (HbA1c), total cholesterol (TC), low-density lipoprotein cholesterol (LDL cholesterol), high-density lipoprotein cholesterol (HDL cholesterol), triglycerides (TG), and C-reactive protein. The HbA1c cutoff of 7% set by the American Diabetes Association was used to establish therapeutic targets [18]. Thus, participants were sorted into two groups according to their HbA1c levels: responders and non-responders.

Statistical Analysis

After being double-checked for accuracy, the research's data was inputted into an electronic database and analyzed using IBM's SPSS version 26 software. The frequencies and/or percentages were used to display discrete variables, whereas continuous variables were given as means with their corresponding standard deviations. The cutoff for statistical significance was set at 0.05, or less ($P \leq 0.05$). Independent sample T-tests determined the significance of mean differences between two independent variables. The significance of variations between the means of three or more unrelated groups was investigated using a one-way ANOVA test. The chi-square test was used to display and analyze the categorical information.

Results

Table (1) illustrates the socio-demographic and related characteristics of patients. This study involved 80 patients (N = 80), and the patients' ages varied from 33 to 65 years, with a mean of 51.7±9 years, and around one-third aged 50–60 years. Regarding gender distribution between participants, the female-to-male ratio was 1.11:1. Only five patients (6.3%) were normal weight, and 93.7 were overweight or obese. Out of the total study patients, 50 (62.5%) were hypertensive.

Table (1): Socio-demographic and related characteristics of patients

Characteristics		**Total=80 No. (%)**
Age (in years)	mean ±SD	51.7±9
	Range	33- 65
Age groups (years)	< 40	8 (10)
	40- 49	23 (28.8)
	50-59	27 (33.8)
	≥ 60	22 (27.4)
Gender	Female	42 (52.5)
	Male	38 (47.5)
BMI	Normal weight	5 (6.3)
	Overweight	39 (48.7)
	Obese	36 (45)
Duration of diabetes (years)	mean ±SD	6.6±3.2
	Range	1- 13
Dieting	Not on diet	43 (53.8)
	On diet	37 (46.2)
Lifestyle	Active	51 (63.8)
	Sedentary	29 (36.2)
Smoking	No	63 (78.8)
	Yes	17 (21.2)
Hypertension	Yes	50 (62.5)
	No	30 (37.5)

Continuous parameters were represented as mean ± SD; Discrete parameters were represented as numbers and frequencies; BMI: body mass index

The response rate to treatment among the included patients was illustrated in Figure (1). Responders were those with HbA1c levels less than 7, while those with HbA1c levels equal to or greater than 7 were considered non-responders. Poor response was seen in a majority of patients (56.2%, n=45) compared to good response (43.8%, n=35).

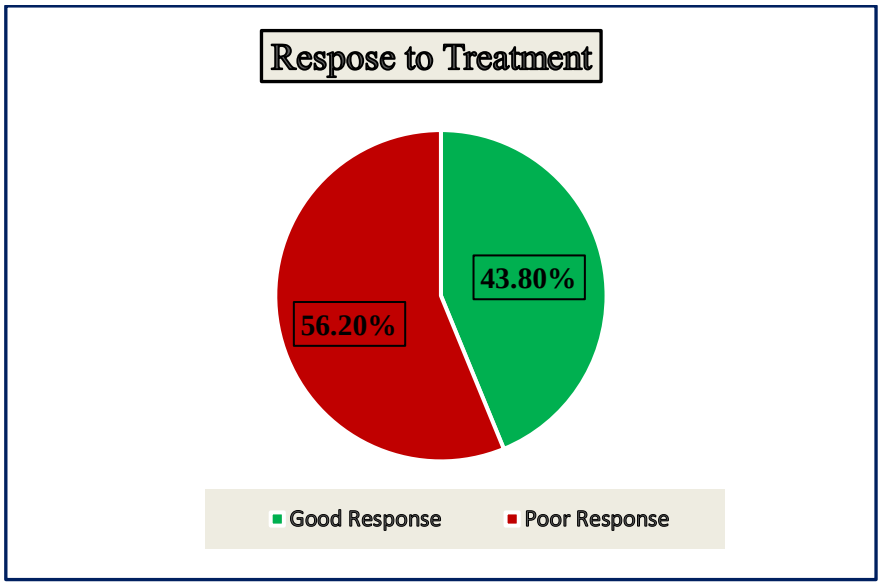

Figure (1): Proportions of response to treatment among study patients

The significance of mean differences of HbA1c based on different demographic and clinical variables was shown in Table (2). Smokers and hypertensive patients, in addition to those not on diet, had higher HbA1c levels with nearly significant p-value than non-smokers, normotensive patients, and those on diet, respectively.

Table (2): Mean HbA1c levels based on patient's demographic and clinical data

Variable		HbA1c Mean ± SD	P value
Age groups (years)	< 40	6.73±1.42	0.542 [1]
	40- 49	7.22±1.37	
	50-59	7.48±1.09	
	≥ 60	7.25±1.35	
Gender	Female	7.15±1.29	0.385 [2]
	Male	7.40±1.26	
Weight status based on BMI	Normal weight	6.98±1.00	0.815 [1]
	Overweight	7.34±1.24	
	Obese	7.23±1.36	
Duration of diabetes	≤ 5 years	7.02±1.22	0.11 [1]
	6-10 years	7.54±1.34	
	> 10 years	7.60±0.86	
Diet	Not on diet	7.52±1.29	0.058 [2]
	On diet	6.98±1.21	
Life style	Active	7.28±1.21	0.94 [2]
	Sedentary	7.26±1.40	
Smoking	Yes	7.79±1.14	0.058 [2]
	No	7.13±1.28	
Hypertension	Yes	7.47±1.31	0.054 [2]
	No	6.90±1.14	

[1]: One-way ANOVA; [2]: Independent samples t-test; significant P value of less than 0.05

Biochemical parameters were compared between patients who had a good response and those who had a poor response to treatment, and the results were displayed in Table (3). There was a statistically significant difference in terms of total cholesterol, triglycerides, and VLDL cholesterol.

Table (3): Mean biochemical parameters of good and poor response patients

Variables	Categories	Response		P value
		Good response (n=35)	Poor response (n=45)	
C-reactive protein	Mean ±SD	5.19±1.54	6.93±6.6	0.136
Total cholesterol	Mean ±SD	168.27±27.68	195.15±15	**0.002***
Triglycerides	Mean ±SD	135.65±68.46	207.44±74.89	**0.001***
HDL-cholesterol	Mean ±SD	39.48±7.75	37.73±8.43	0.343
LDL-cholesterol	Mean ±SD	101.66±26.59	115.93±35.66	0.052
VLDL- cholesterol	Mean ±SD	27.13±4.38	41.48±14.97	**0.001***

Independent samples t-test was used with a significant P value of less than 0.05; *: highly significant (P value <0.01)

Discussion

With regard to the age factor, only 8 patients (10% of the study population) were under 40 years of age, while the rest (N = 72,90%) were over 40. Most of those over 40 years of age are in the 50–59 age group, which represents 33.8% of all participants in this study, as shown in Table (1). This

age distribution of the population study was consistent with a study in Basra, south of Iraq, that involved 5445 people and showed that diabetes prevalence in both genders reached its peak between the ages of 46 and 60 [19]. With respect to the weight status of patients who participated in this study, only 5 (6%) patients have a normal weight; the rest were overweight (39 patients; 48.7%) or obese (36 patients; 45%), and they collectively represent approximately 94% of the total number of participants. This high prevalence of abnormal weight status (overweight or obesity) within the study's population was consistent with the established association between T2D and obesity. They're connected by a connection that goes into a vicious circle so that they can both lead to each other. In T2D, insulin secretion, action, or both are deficient, and because insulin regulates the metabolism of carbohydrates, proteins, and fats, resistance to insulin is often related to obesity. On the other hand, adipose tissue in obese people may contribute to the development of insulin resistance by secreting excess amounts of non-esterified fatty acids, glycerol, hormonal substances, and pro-inflammatory mediators [20]. Although hypertension and T2D can be identified easily, they are actually quite complex and heterogeneous phenotypes. The common occurrence of both illnesses in the same individual is not a chance given the overlapping pathophysiology between them, especially with regard to the pathological mechanisms associated with excessive body weight and resistance to insulin. With regard to hypertension prevalence, those with T2D are up to three times more likely to have hypertension than those without the disease [21–23]. The overlapping disease mechanisms explain why diabetes patients tend to have high blood pressure; it was observed in this study that 62.5% of patients had hypertension.

With respect to smoking, mean HbA1c measurements were elevated in smokers compared to non-smokers (7.79±1.14 vs. 7.13±1.28), as shown in Table (2). These results were in accordance with a study that included an overall number of 120 patients diagnosed with T2D to explain the impact of smoking and nicotine dependency on the levels of glycated hemoglobin A1c. The study showed that smokers had higher levels of HbA1c, and the nicotine dependence test result had a positive relationship with HbA1c [24]. While the current study did not find a statistically significant link between smoking and HbA1c levels (P-value = 0.058), the observation of higher HbA1c levels in smokers' patients is still important, and further investigation using a larger sample size may be warranted. In another study that included 60 T2D participants, the findings showed that smoker diabetic patients have higher HbA1c levels than non-smoker diabetic patients, but this difference did not reach significant levels [25]. These elevations in HbA1c may be partially explained by the detrimental effects of smoking on glucose metabolism and insulin production [26]. Cigarette smoke increases oxidative stress. Peroxidation of fatty acids, oxidation of proteins, and destruction of DNA are all forms of oxidative damage brought on by this scenario. The pancreatic island is especially susceptible to damage caused by reactive oxygen species. This is exacerbated by a deficiency of cellular antioxidant enzymes. The pancreatic island is especially susceptible to cell damage from reactive oxygen species and a lack of antioxidant enzymes [25].

The current study observed that the mean HbA1c levels of individuals with hypertension were higher than those of patients with normal blood pressure (7.471.31 vs. 6.901.14, P-value = 0.054), as explained in Table (2). These results did not reach a significant level but were still important. Clinical determinants of DPP-4 inhibitor response were investigated in a study involving 662 individuals with T2D who were treated with DPP-4 inhibitors. According to the study, the probability of having a favorable response to DPP-4 inhibitor treatment increased by 1.7 times

among patients with diastolic blood pressure below 90 mmHg compared to those with higher diastolic blood pressure readings. The study concluded that diastolic blood pressure may be a clinical predictor of response to DPP-4 inhibitor treatment [27]. While the sample size and analysis methods of the current study were different from the mentioned studies, the general observation from these studies was that people with high blood pressure were unlikely to respond well to therapy with DPP-4 inhibitors. Based on their common presentation, patients with diabetes often have comorbidities such as hypertension. A study that included 65 patients was done to examine the effects of patient characteristics such as hypertension and genetic variability on the response to the gliptin sitagliptin. In view of the results of the study, people with T2D and hypertension respond less favorably to sitagliptin's DPP4 inhibition than did normotensive T2D patients. The study established that sitagliptin at 100 mg/d did not fully inhibit DPP4 in patients with T2D and hypertension [28].

Poor responders to sitagliptin had significantly higher mean levels of total cholesterol, triglycerides, and VLDL-cholesterol compared to good responders, As shown in Table (3). The results of the current study were consistent with those of another study, in that HbA1c was positively correlated with TC, TG, and LDL-cholesterol. There was no statistically significant relationship between HbA1c and HDL- cholesterol [29]. Several variables, including insulin insufficiency or resistance, adipocytokines, and hyperglycemia, may account for the dysfunction in the metabolism of lipids reported in diabetic individuals. The pathogenesis of diabetic dyslipidemia remains in doubt, while hypertriglyceridemia's mechanism is well established [30].

A study by Matikainen *et al*. established that DPP-4 inhibitors improve postprandial lipid levels, particularly postprandial plasma TG, after a lipid-rich meal. A high level of DPP4 expression may be found in human adipocytes, and this level of expression is further elevated in the subcutaneous and visceral adipose tissue of obese people [31]. Using a nonobese mouse model of T2D, Shirakawa *et al.* studied the influence of DPP-4 inhibition on adipocytes and discovered that DPP-4 inhibitors enhanced linoleic acid-induced adipose tissue hypertrophy [32]. These studies supported the current study's finding that sitagliptin improves lipid parameters overall, including TG so poor response to sitagliptin was associated with high TG levels in T2D patients and high TG levels may be a predictor of poor response to sitagliptin.

Limitations

The current study has some limitations. Because of the relatively small sample size, the findings of this study need to be replicated and confirmed in larger studies. Furthermore, it was challenging to rule out all potential confounding effects of co-morbidities and concomitant medications.

Conclusions:

- Smoking T2D patients had higher HbA1c levels than non-smokers, which explains the detrimental effects of smoking on glucose metabolism and insulin production.
- Type 2 diabetic patients with high blood pressure were likely to have a weak response to DPP-4 inhibitor treatment given that hypertensive patients had higher HbA1c levels than normotensive patients.
- Type 2 diabetic patients not on a healthy diet were likely to have a poorer response to DPP-4 inhibitor treatment with higher HbA1c levels compared to those on a healthy diet.
- Elevated levels of TG may serve as an indicator of poor response.

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