https://doi.org/10.46389/rjd-2020-1057
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2020; volume 27, issue 4, pages 396-402

Original Research

Prescribing pattern of dipeptidyl peptidase 4 inhibitors and level of HBA1C target achievements among outpatients with type 2 diabetes mellitus in a Malaysian university teaching hospital

Mohamed Hassan Elnaem[1,2]*, Mohamad Hafiz Hakeem Shamsuri[1], Nur Athirah Mohamad Aziz[1], Nurul Iman Alias[1], Rauha Farhana Hafizi[1], Nur Faezah Latif[1], Arina Norhazwani Rashid[1], Mohd Faris Aiman Mohamad Jalil[1], Mery Wei Ying Hu[3]

[1] Department of Pharmacy Practice, Faculty of Pharmacy, International Islamic University Malaysia, Kuantan, Pahang, Malaysia
[2] Quality Use of Medicines Research Group, Faculty of Pharmacy, International Islamic University Malaysia, Kuantan, Pahang, Malaysia
[3] Department of Pharmacy, Sultan Ahmad Shah Medical Centre@ IIUM, Kuantan, Pahang, Malaysia

*Correspondence to: Mohamed Hassan Elnaem, PharmD, PhD, Department of Pharmacy Practice, Faculty of Pharmacy, International Islamic University Malaysia, 25200 Kuantan, Pahang, Malaysia. E-mail: drmelnaem@gmail.com, drmelnaem@iium.edu.my. Phone: 0060193944726, 00695714600

Received: 25 March 2020 / Accepted: 20 June 2020

Abstract

Background and Aims: Oral antidiabetic drugs, including Dipeptidyl Peptidase 4 Inhibitors (DPP4i), are the mainstay for therapeutic management of type 2 diabetes mellitus (T2DM). We aimed to describe the prescribing pattern of DPP4i agents and to assess the achievement of the target HbA1c levels among current DPP4i users at a Malaysian University teaching hospital. **Material and Method:** A retrospective cross-sectional study was conducted in the outpatient diabetes clinic of a university teaching hospital in Pahang, Malaysia. The data included adults with T2DM who received DPP4i prescriptions at least three months before December 2019 and reported data of HbA1c after at least three months from the index date. Evaluation of the DPP4i prescribing patterns referred to the national clinical practice guidelines. **Results:** 140 cases were included. Sitagliptin 50 mg is the most commonly prescribed DPP4i regimen (72.1%), and its combination therapy with metformin contributed to 67.1% of the total DPP4i prescriptions. About 35% of patients achieved their target HbA1c levels after at least three months on DPP-4 inhibitors therapy. There was no significant association between the type of DPP4i and the target HbA1c achievement (p=0.205). **Conclusions:** DPP4i medications were more prescribed as combination therapy with metformin, compared to monotherapy except for vildagliptin. Gliclazide was the most common co-prescribed OAD with vildagliptin. Barriers to achieving optimal glycemic control for patients on OAD, particularly DPP4i, need further investigations.

Keywords: Dipeptidyl Peptidase 4 Inhibitors, glycemic control, Malaysia, Oral antidiabetic drugs, type 2 diabetes mellitus.

Background and Aims

Diabetes mellitus remains one of the major concerns in Malaysia with a reported prevalence of 17.5% in 2015, the majority of them are type 2 diabetes mellitus (T2DM) cases [1]. The pharmacotherapy of T2DM is directed towards alleviating the symptoms, achieving the target glycemic levels of patients, and preventing complications [2]. One of the common markers used in monitoring the glycemic level is Hemoglobin A1c (HbA1c), which gives a long term profile of diabetes control [3]. Oral antidiabetic drugs (OAD), including Dipeptidyl Peptidase 4 Inhibitors (DPP4i), are the mainstay for the therapeutic management of patients with T2DM. Through their impact

on elevating incretin hormones, DPP4i showed clinical significance to stimulate insulin release among patients with T2DM [4]. The use of DPP4i agents (sitagliptin, vildagliptin, linagliptin, and saxagliptin) in combination with other OADs or insulin is widely accepted because of their established tolerability and safety profiles [2].

In a study aimed to assess the effectiveness of DPP4i in clinical practice, the findings highlighted that sitagliptin use was associated with a significant reduction in HbA1c over the first six months in a pattern consistent with reported observations from clinical trials [5]. In addition, a systematic review looked at the extent of effectiveness of T2DM add-on therapies; the significant impact of DPP4i agents on attaining glycemic control was reported [6]. Furthermore, the use of DPP4i among patients with T2DM who had high cardiovascular and renal risk seems to be safe, and newer agents, e.g., linagliptin, may even be offered for renal patients with no need for dose adjustment [7]. Therefore, previous findings have underpinned a significant association between the use of DPP4i among patients with T2DM who were concurrently receiving cardiovascular medications such as beta-blockers and aspirin [8].

In most of the diabetes clinical guidelines, there are recommendations for the preferred use of specific OAD agents based on patients' characteristics and comorbidities [9]. Therefore, it is essential to investigate the quality use of OAD in the clinical setting by reporting the prescribing patterns and the associated achievement of favorable outcomes. In this research, we aimed to describe the prescription pattern of DPP4i among outpatients with T2DM at a university teaching hospital. Also, the assessment of the DPP4i use concerning the level of achievement of target HbA1c values was performed.

Material and Method

Study design and patients

A retrospective cross-sectional study was conducted. The data of patients receiving DPP4i in IIUMMC was collected from the hospital database through a prescribing period from March to September 2019 to ensure that the data of the latest HbA1c level of the patients could be obtained. We included data of adults with T2DM who received DPP4i prescriptions at least three months before the data collection and reported HbA1c after at least three months from the index date. Patients who received new in-ward DPP4i prescriptions and those who did not have reported HbA1c after at least three months from the index date were excluded. Initially, 1218 prescriptions of DPP4i during the period of data collection were screened. Following further exclusion of the in-ward prescriptions and patients not in line with the inclusion criteria, 191 prescriptions were identified. By considering the availability of the HbA1c results after at least three months, the final sample included 140 patients.

Outcome Measures

The assessment of the DPP4i use and the associated glycemic control achievement was determined according to the target levels classified by the Ministry of Health in the clinical practice guidelines (CPG) Management of Type 2 Diabetes Mellitus (5th Edition), as shown in Table 1.

Ethical Requirements

The study proposal has obtained ethical approval from the university institutional review board, IIUM Research Ethics Committee (IREC), before starting the data collection procedures. The study approval ID was IREC 2019–229. All ethical considerations were strictly abided by the research team throughout the research process.

Statistical analysis

Descriptive statistical analysis using frequencies and mean value for characteristics of the study population and HbA1c was used. In addition, inferential statistics using Chi-Square Test was employed to test for any significant

Table 1: Target HbA1clevels according to patients' characteristics and underlying conditions [2].

Individualized HbA1ctargets and patients' profile		
Tight (6.0–6.5%)	**6.6–7.0%**	**Less tight (7.1–8.0%)**
• Newly diagnosed • Younger age • Healthier (long life expectancy, no CVD complications) • Low risk of hypoglycemia	• All others	• Comorbidities (coronary disease, heart failure, renal failure, liver dysfunction) • Short life expectancy • Prone to hypoglycemia

association between the DPP4i types, prescribing pattern with the achievement of glycaemic control. The significant association was denoted at ($p<0.05$). All analyses were done using Statistical Package for the Social Sciences (SPSS) version 23.

Results

From the finally included sample of 140 patients receiving DPP4i in IIUMMC outpatient pharmacy, 61 patients were female, and 137 of them were Malay race. About 90% of participants received DPP4i as a combination therapy with other OAD. It was observed that 41.4% of males and 30.7% of female patients were given sitagliptin 50 mg. In comparison, the least prescribed DPP4i was vildagliptin 50 mg, with a percentage of 4.3% and 8.6% for females and males, respectively. There were no statistically significant differences between gender, race, and the type of prescribed DPP4i. Besides, most of the T2DM patients prescribed with DPP4i were in the age group of 58–67 years old (40%). There were no statistically significant differences between the age groups of the patients and the type of prescribed DPP4i. A large proportion of patients who were prescribed with sitagliptin 50 mg were overweight. normal. Meanwhile, obese patients were receiving more prescriptions of sitagliptin 100 mg. Figure 1 shows a graphical presentation of the prescribed DPP4i regimens according to the patients' body mass index (BMI). There was a statistically significant difference between the patient's BMI and the type of prescribed DPP4i (p-value = 0.024). The prescribing pattern of DPP4i concerning patients' characteristics is illustrated in Table 2.

Co-administered drugs with DPP4i

The findings showed that statin (85.7%) was the most frequently co-administered drug with DPP4i of the patients who were prescribed both statin and DPP4i. Next, antihypertensive therapy (72.9%) was the second most common co-administered drug with DPP4i. Besides, vitamins and supplements were found in 40% of the DPP4i prescriptions with a relatively higher percentage among vildagliptin users. Other medications, such as antiplatelet therapy and proton pump inhibitors, were also often co-administered with DPP4i in 35.8% and 20.7% of prescriptions, respectively. A similar percentage of patients (10%) were reported for anti-gout and anti-epileptic medications. Concerning the co-administered DM pharmacotherapy, metformin (64.1%) was the most common co-administered OAD with DPP4i, followed by gliclazide, and empagliflozin with reported percentages of 43.6% and 22.1%, respectively. For patients who were taking sitagliptin 50 mg and 100 mg, the most common co-administered OAD is metformin with a percentage of 47.9% and 12.9%, respectively. Meanwhile, gliclazide is the most common co-administered OAD for patients prescribed with vildagliptin 50 mg. Also, the most common insulin co-administered to the DPP4i receivers was Insulin Detemir (17.1%). In comparison, Ryzodeg "Insulin degludec 2.56 mg, insulin aspart 1.05 mg per ml" (2%) was the least common co-administered insulin among patients on DPP4i prescriptions.

Achievement of glycemic control

As an indicator of glycemic control in T2DM patients, the HbA1c levels of the included

https://doi.org/10.46389/rjd-2020-1057

Table 2: Prescribing pattern of DPP4i with patients' characteristics

Variable	Type of DPP-4 inhibitors			Total
	Sitagliptin 50 mg	Sitagliptin 100 mg	Vildagliptin 50 mg	
Prescription pattern				
Monotherapy	7 (5.0%)	0	7 (5.0%)	14 (10%)
Combination therapy	94 (67.1%)	21 (15.0%)	11 (7.9%)	126 (90%)
Gender				
Female	43 (30.7%)	12 (8.6%)	6 (4.3%)	61 (43.6%)
Male	58 (41.4%)	9 (6.4%)	12 (8.6%)	79 (56.4%)
Race				
Malay	99 (70.7%)	21 (15.0%)	17 (12.1%)	137 (97%)
Chinese	0	0	1 (0.7%)	1 (0.7%)
Indian	2 (1.4%)	0	0	2 (1.4%)
Age				
28–37 years	2 (1.4%)	0	0	2 (1.4%)
38–47 years	9 (6.4%)	1 (0.7%)	2 (1.4%)	12 (8.6%)
48–57 years	27 (19.3%)	7 (5.0%)	5 (3.6%)	39 (27.9%)
58–67 years	41 (29.3%)	10 (7.1%)	5 (3.6%)	56 (40%)
68–77 years	20 (14.3%)	3 (2.1%)	3 (2.1%)	26 (18.6%)
78–87 years	2 (1.4%)	0	3 (2.1%)	5 (3.6%)
Body Mass Index (BMI)				
<18 (underweight)	0	0	0	0
18.5–24.9 (normal)	23 (16.4%)	3 (2.1%)	5 (3.6%)	31 (22.1%)
25–29.9 (overweight)	41 (29.3%)	5 (3.6%)	5 (3.6%)	51 (36.4%)
>30 (obese)	31 (22.1%)	11 (7.9%)	3 (3.6%)	45 (32.1%)

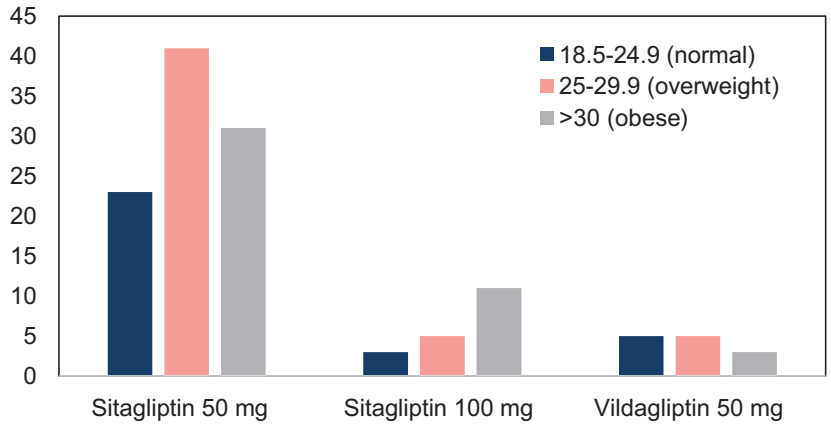

Figure 1: Prescribing pattern of DPP-4 inhibitors according to the BMI of the patient

patients were recorded. The mean values of HbA1c before the initiation of DPP-4 inhibitor therapy, after three months and six months, were 9.0 ± 2.2, 8.0 ± 2.0, and 8.2 ± 1.9, respectively. The result shows that 35% (N=49) of the patients taking DPP-4 inhibitors achieved within target values of HbA1c. Table 3 shows the overall association of DPP4i regimens with their reported HbA1c measures.

Among those 101 patients who are on current sitagliptin 50 mg prescription, only 36.6% of them manage to reach the HbA1c target, whereby the patients who were given combination therapy with other OAD contributed the highest percentage (22.8%). Also, about 45% of patients who were taking vildagliptin 50 mg had achieved the HbA1c target; of them, 33.3% were on monotherapy. Table 4 demonstrates the details of the

Table 3: Target achievement of the HbA1c levels.

Type of DPP-4 inhibitors	HbA1clevel within the target		HbA1clevel out of the target	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Sitagliptin 50 mg	37	26.4	64	45.8
Sitagliptin 100 mg	4	2.9	17	12.1
Vildagliptin 50 mg	8	5.7	10	7.1
Total	**49**	**35.0**	**91**	**65.0**

Table 4: Target of HbA1c level achieved with the use of DPP-4 inhibitors.

Prescribing pattern	Percentage of patients that reach the HbA1c target (%)		
	Sitagliptin 50 mg (n= 37 out of 101)	Sitagliptin 100 mg (n= 4 out of 21)	Vildagliptin 50 mg (n= 8 out of 18)
Monotherapy	5.9	0	33.3
Combination therapy with insulin only	2.0	0	11.1
Combination therapy with other OAD only	22.8	19.0	0
Combination with insulin and other OAD	5.9	0	0
Percentage of patients reach HbA1c target (%)	36.6	**19.0**	**44.4**

Table 5: A summary of variables with a significant association with the type of DPP4i

Variables	P-value (p<0.05)
Prescription pattern	0.000
Body Mass Index (BMI)	0.024
Co-administered drug (vitamin and supplement)	0.008
Co-administered OADs (metformin)	0.000

prescribed DPP4i patterns within the cases that have achieved HbA1c values. Finally, the variables listed in Table 5 showed statistically significant association with the type of the prescribed DPP4i

Discussion

Type of DPP-4 Inhibitors Therapy Commonly Prescribed in the Study Setting

Sitagliptin and vildagliptin were the only two types of prescribed DPP4i in the study setting. Overall results showed more prescriptions of DPP4i combination therapy compared to monotherapy. It might be explained by the superior HbA1c reduction of sitagliptin/metformin combination compared to monotherapy of each drug [10]. Also, it was reported that the use of sitagliptin 100 mg as add-on therapy to 1000 mg metformin reduced HbA1c by 0.9% over 24 weeks among Chinese patients with T2DM following inadequate glycemic control with metformin alone [11]. Moreover, it is well established that metformin is the mainstay in the monotherapy treatment initiation, and other OAD, e.g., DPP4i, will be considered in case of inadequate control [2]. Therefore, the patterns observed in this study seem to be in line with the clinical guidelines.

Vildagliptin was the least prescribed DPP4i among our study participants despite the evidence that its associated HbA1c reduction was comparable to that of sitagliptin [12]. Also, the percentage of patients on vildagliptin monotherapy was relatively higher than that of siltagliptin monotherapy. In contrast, a previous study reported an overall low utilization of vildagliptin monotherapy [8]. The prescribing of DPP4i

https://doi.org/10.46389/rjd-2020-1057

monotherapy could be noticed among patients with renal problems and those with severe heart failure in whom metformin therapy will not be an appropriate therapeutic choice [13].

Common Co-Administered Drugs with DPP-4 Inhibitors

Vildagliptin was frequently prescribed for the patient receiving calcitriol or ferrous fumarate supplement. The dosage of vildagliptin should be halved from 100 mg twice daily to 50 mg once daily in a patient with moderate to severe renal impairment [14]. Although our work did not trace for the concurrent comorbidities extensively, it is noticeable that these supplements for vitamin D deficiency and iron-deficiency anemia can be seen in a patient with chronic kidney disease (CKD). Moreover, vildagliptin is more preferred in a patient with CKD compared to sitagliptin due to its favorable pharmacokinetic properties [14, 15]. Only 23% of orally ingested vildagliptin excreted unchanged in the urine, whereas most of the ingested sitagliptin exclusively excreted unchanged in the urine [14].

Next, DPP4i was frequently prescribed in combination therapy with gliclazide in line with the recommendations of CPG on the management of T2DM [2]. Gliclazide is a preferred sulfonylurea as a second-line OAD because of its relatively safer CV profile for and less incidence of hypoglycemia compared to the other sulfonylureas [16]. In contrast, glibenclamide has shown an undesirable effect on type 2 diabetes mellitus patients with coronary artery disease [17]. From the medications screening, it was clear that many patients had a comorbid cardiovascular disease, which could explain the frequent use of DPP4i in combination therapy with gliclazide.

Type of the Prescribed DPP4i among Patients with Different BMI

According to the statistics released by the National Diabetes Registry Report in 2012, 83.4% of the diabetic patients were also overweight or obese [2]. Thus, a prescriber needs to consider the impact of OAD on weight gain. According to the national clinical practice guidelines for the management of T2DM, metformin is the first-line agent for patients with normal, overweight, and obese BMI. DPP-4 inhibitor is considered a second-line choice for normal and overweight patients and the fourth line in obese [2]. The findings showed frequent use of sitagliptin, which is preferred in overweight patients compared to thiazolidinediones and sulphonylureas due to its weight neutral properties [5]. However, for obese patients, other antidiabetic agents such as SGLT2i and GLP-1 receptor antagonists that could promote better glycemic control in obese patients compared to sitagliptin [18]. It is suggested that the choice of the add-on OAD therapies should consider the individual patients' conditions carefully to give the optimal glycemic control and avoid unwanted health outcomes.

The Level of HbA1c Target Achievement with DPP-4 Inhibitors Therapy

Overall, the use of both sitagliptin and vildagliptin can achieve glycemic control. Based on the previous study, 66% of patients who received sitagliptin 100 mg as combination therapy with metformin 2000 mg achieved HbA1c target less than 7% [19]. In comparison with our findings, the prescribed doses were relatively lower. Nevertheless, a still considerable number of patients on sitagliptin combination therapy could achieve glycemic control.

Among the relatively low number of cases on vildagliptin therapy, the majority has achieved the target HbA1c. This was consistent with prior evidence regarding the extent of attaining target HbA1c after four months on vildagliptin monotherapy [20]. With greater focus, it has been reported in our findings that a more substantial proportion of patients failed to achieve target HbA1c. Considering the lack of investigation of all the barriers related to the achievement of target HbA1c, we could only suggest that better glycemic control could be achieved through

addressing patients' non-compliance to medications, insufficient treatment, and non-adherence to therapeutic lifestyle changes.

Conclusions

The DPP4i were more prescribed as combination therapy, mainly with metformin, compared to monotherapy except for vildagliptin. Gliclazide was the most common co-administered OAD with vildagliptin. Overall, only one-third of patients prescribed with DPP4i were able to achieve target HbA1c values. Barriers to achieving optimal glycemic control for patients on OAD, particularly DPP4i, need further investigations.

Limitations

There were several limitations upon the completion of this research. One limitation was time constraints because of the short period specified for executing all data collection procedures. Also, there was a difficulty in accessing the data of patients before they started to receive diabetes care in the hospital, which may affect the accuracy of the data related to the exact date of DPP4i initiation.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Tee ES, Yap RWK. Type 2 diabetes mellitus in Malaysia: Current trends and risk factors. *Eur J Clin Nutr*. 71: 844–849, 2017.
2. Health M of. *Clinical Practice Guidline: Management of Type 2 Diabetes Mellitus*. 5th ed. Putrajaya: Ministry of Health Malaysia, 2015.
3. Sherwani SI, Khan HA, Ekhzaimy A, et al. Significance of HbA1c test in diagnosis and prognosis of diabetic patients. *Biomark Insights*. 11: 95–104, 2016.
4. Gallwitz B. Clinical use of DPP-4 inhibitors. *Front Endocrinol (Lausanne)*. 10: 1–10, 2019.
5. Dallumal RM, Chua SS, Wu DBC, et al. Sitagliptin: Is it effective in routine clinical practice? *Int J Endocrinol*. 2015: 1–9, 2015.
6. Wong MCS, Wang HHX, Kwan MWM, Zhang DDX, Liu KQL, Chan SWM, et al. (2014) Comparative Effectiveness of Dipeptidyl Peptidase-4 (DPP-4) Inhibitors and Human Glucagon-Like Peptide-1 (GLP-1) Analogue as Add-On Therapies to Sulphonylurea among Diabetes Patients in the Asia-Pacific Region: A Systematic Review. PLoS ONE 9(3): e90963. https://doi.org/10.1371/journal.pone.0090963
7. Hanssen NMJ, Jandeleit-Dahm KAM. Dipeptidyl peptidase-4 inhibitors and cardiovascular and renal disease in type 2 diabetes: What have we learned from the CARMELINA trial? *Diabetes Vasc Dis Res*. 16: 303–309, 2019.
8. Hasniza Zaman Huri, NorFarahen Selamat, Shireene Ratna Vethakkan, "Factors Associated with Utilization of Dipeptidyl-4 Inhibitors in Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Retrospective Study", *International Journal of Endocrinology*, vol. 2014, Article ID 367564, 7 pages, 2014. https://doi.org/10.1155/2014/367564
9. Reusch JEB, Manson JE. Management of Type 2 Diabetes in 2017. *Jama*. 317: 1015, 2017.
10. Hayes J, Anderson R, Stephens JW. Sitagliptin/metformin fixed-dose combination in type 2 diabetes mellitus: An evidence-based review of its place in therapy. *Drug Des Devel Ther*. 10: 2263–2270, 2016.
11. Yang W, Guan Y, Shentu Y, et al. The addition of sitagliptin to ongoing metformin therapy significantly improves glycemic control in Chinese patients with type 2 diabetes. *J Diabetes*. 4: 227–237, 2012.
12. Marfella R, Barbieri M, Grella R, et al. Effects of vildagliptin twice daily vs. sitagliptin once daily on 24-hour acute glucose fluctuations. *J Diabetes Complications*. 24: 79–83, 2010.
13. Davoren P. Safe prescribing of metformin in diabetes. *Aust Prescr*. 37: 2–5, 2014.
14. He YL, Kulmatycki K, Zhang Y, et al. Pharmacokinetics of vildagliptin in patients with varying degrees of renal impairment. *Int J Clin Pharmacol Ther*. 51: 693–703, 2013.
15. Ministry of Health (New Zealand). *Medsafe: DPP4 inhibitors*. 2018.
16. Fadini GP, Bottigliengo D, D'Angelo F, et al. Comparative Effectiveness of DPP-4 Inhibitors Versus Sulfonylurea for the Treatment of Type 2 Diabetes in Routine Clinical Practice: A Retrospective Multicenter Real-World Study. *Diabetes Ther*.9: 1477–1490, 2018.
17. Azimova K, San Juan Z, Mukherjee D. Cardiovascular safety profile of currently available diabetic drugs. *Ochsner J*. 14: 616–632, 2014.
18. Kodera R, Shikata K, Nakamura A, et al. The glucose-lowering efficacy of sitagliptin in obese japanese patients with type 2 diabetes. *Intern Med*. 56: 605–613, 2017.
19. Barry J, Goldstein M, Johnson J, MD B 3, Mark N, Feinglos M, et al. Effect of Initial Combination Therapy With Sitagliptin, a Dipeptidyl Peptidase-4 Inhibitor, and Metformin on Glycemic Control in Patients With Type 2 Diabetes. *Diabetes Care*; 30. Epub ahead of print 2007. DOI: 10.2337/dc07-0627. Clinical.
20. Yavropoulou MP, Pikilidou M, Kotsa K, et al. Efficacy and tolerability of vildagliptin as first line treatment in patients with diabetes type 2 in an outpatient setting. *J Diabetes Metab Disord*. 14: 1–7, 2015.

 https://doi.org/10.46389/rjd-2020-1057