Evaluation of Hypoglycaemic Effects of Dipeptidyl Peptidase–4 Inhibitors and Biguanide on Type-2 Diabetic subjects: A six months trial

Naghma[1], Sadia M Azam Khan[2], Atta Ullah Khan[3], Zahoor Ahmed[4], Muhammad Umar[5], Muhammad Shabbir Khan[6]

[1] Institute of Chemical Sciences, University of Peshawar, Peshawar.
[2] Assistant Professor, Department of Family Medicine, Poonch Medical College, Rawalakot, AJK.
[3] Associate Professor, Department of Medicine, Pak International Medical College, Peshawar.
[4] Associate Professor, Department of Biochemistry, Khyber Medical College, Peshawar.
[5] Vice-Chancellor, Rawalpindi Medical University, Rawalpindi.
[6] Mphil Scholar, Department of Biochemistry, Khyber Medical College, Peshawar.

Author's Contribution	Corresponding Author	Article Processing
[1,4] *Conception of study*	*Dr.Sadia Azam Khan,*	*Received: 25/08/2020*
[1] *Experimentation/Study conduction*	*Associate Professor,*	*Accepted: 05/11/2020*
[1,4] *Analysis/Interpretation/Discussion*	*Department of Family Medicine,*	
[4] *Manuscript Writing*	*Poonch Medical College,*	
[2,3,5,6] *Critical Review*	*Rawalakot*	
[2,5] *Facilitation and Material analysis*	*Email: mksk361@gmail.com*	

Abstract

Objective: This trial was conducted to evaluate the effectiveness of oral hypoglycemic agents on diabetic control and biochemical parameters of known diabetic subjects.

Introduction: T2DM occurs due to abnormal metabolism of carbohydrates, proteins, and lipids leading to increased blood glucose characterized by polyuria and polydipsia due to relative[5] deficiency or lack of insulin. Besides dietary control and insulin therapy, various oral hypoglycemic such as sulfonylurea biguanide, a thiazolidinedione, DPP–4 inhibitors, glucagon-like peptide inhibitors, and SGL2.

Material and Methods: This comparative trial was carried out on previously diagnosed type–2 diabetic subjects. This trial was conducted at health care centers of District Nowshehra viz. NMC Nowshehra, DHQ Hospital Nowshehra, and ICS, Peshawar in collaboration with KMC and PIMC Peshawar, Khyber Pakhtunkhwa, Pakistan. A total of 200 known diabetic subjects were randomly recruited based on predetermined selection criteria and were split into two groups.

Results: Significant results ($p < 0.05$) were seen for glycemic control (FBS, RBS, HbA$_1$C**)** in Group B as compared to Group A patients.

Keywords: Anti-diabetic, HbA1C, Sulfonylurea, DPP–4 Inhibitors

Introduction

Type–2 diabetes (T2DM) occurs due to abnormal metabolism of carbohydrates, proteins, and lipids leading to increased blood glucose characterized by polyuria and polydipsia due to relative deficiency or lack of insulin.[1] T2DM, previously called NIDDM account for up to 90–95 % of diabetes. Type–2 diabetes is an islet paracrinopathy in which mutual connection exists between alpha cells (secrete glucagon) and beta cells (secrete insulin) is abolished which causes increased blood glucose level (hyperglycemia).[2,3] Poor or deficient insulin production increases glycogen breakdown from glucose. In diabetes level of glucose is increased so more influx of glucose occurs than outflow. Abnormal functioning of islet cells is an important character of type–2. In type–2 diabetes increased hepatic glucose production occurs due to hypersecretion of glucagon.[4] In obese type–2 diabetic patients insulin resistance is increased in the liver, muscles, adipose tissue, myocardium, overproduction, and underutilization of glucose occurs.[5] According to the International Diabetes Federation (IDF) known patients of type–2 diabetes were 336 million in 2011 and this number will exceed up to 552 million by 2030.[6]

Obesity and overweight are major risk factors for metabolic syndrome which is an important bunch of coronary heart disease (CAD) risk factors, like high blood pressure, diabetes mellitus, and dyslipidemia.[7-9] A large number of research studies have revealed that subjects with deranged metabolism are at a high risk of future development of type–2 diabetes mellitus.[10,11] T2DM is strongly associated with overweight and obesity.[12,13] A positive link between body mass indexes (BMI), lipids, glucose, and blood pressure have been formerly reported.[14–16] The death rate in diabetic individuals is 2 times more than individuals of the same age.[17] In 2015 in the US diabetes is the l7th leading cause of death.[18] Discovery of insulin in the 19th century comprised as a milestone for the control of glucose. Various oral hypoglycemic agents such as sulfonylurea, biguanide, thiazolidinedione, DPP–4 Inhibitors, glucagon-like peptide (GLP–1 Inhibitors), and SGL2 (Sodium Potassium Co–transport Inhibitors) are used to treat T2DM. DPP–4 inhibitors act by breaking down peptides like glucose-dependent insulinotropic polypeptide (GIP) and GLP–1. DPP–4 inhibitors (discovered in 1966) are used as monotherapy or it can be used also with biguanide or with a thiazolidinedione. All drugs in this class are weight neutral. Common drugs of this class are Sitagliptin, Vildagliptin, Saxagliptin, and Linagliptin[19]. Biological engrossment for the use of dipeptidyl peptidase escalates after acquiescence of DDP–4 inhibitors as pharmacological agents for the treatment of type–2 diabetes. Many reviews have enlightened the effectiveness of using DPP–4 inhibitors as a treatment therapy for type–2 diabetes[13]. DPP–4 inhibitors are renal and cardiac friendly[20-23]. Biguanide is an oral hypoglycemic drug acting by decreasing peripheral insulin resistance decreases morbidity and mortality in T2DM. Further studies illustrated sustained glucose control in diabetic subjects treated with DPP–4 inhibitors alone or in combination with biguanide.[24]

Materials and Methods

This comparative study was carried out on previously diagnosed type–2 diabetic subjects. This study was conducted at health care centers of District Nowshehra viz. Nowshehra Medical Complex (NMC) Nowshehra, District Head Quarter (DHQ) Hospital Nowshehra, and Institute of Chemical Science (ICS), Peshawar in collaboration with Khyber Medical College and Pak International Medical College (PIMC), Peshawar, Khyber Pakhtunkhwa (KPK), Pakistan. A total of 200 known diabetic subjects were randomly recruited based on predetermined selection criteria and were divided into two groups. The first group (Group A) having 100 diabetic subjects was given DPP‑4 inhibitor; Sitagliptin 50 mg two times a day alone for six (06) months while the second group (Group B) comprising of 100 patients were treated with a combination of DPP-4 inhibitor (Sitagliptin 50 mg 1 BD) and metformin in a dose of 500 mg two times a day. Venous blood samples were taken from all participants in both fasting (10–12 hour night long fast) and random (2 hours post-prandial) state. FBS, RBS, HbA_1C, S. creatinine, blood urea, fasting lipid profile, and serum electrolytes were determined by spectrophotometric colorimetric methods using kits (procured from Elitech, Spain) at 03 and 06 months follow up. LDL–c was determined by Fried Wald's formula. Inclusion criteria were that patients with T2DM of age 18years and above were included. T2DM patients on insulin, diabetic nephropathy, and retinopathy were excluded. The study was approved by the Ethical Board of the University of Peshawar. The data was analyzed by using SPPS software version 20.

Results

Table 1 reveals the correlation of various demographic parameters and highly significant differences (p < 0.001) were found for age, BMI, SBP, and pulse respectively. Table 2 reveals the effects of the use of anti-diabetic drug DPP–4 inhibitors alone. The Mean $\pm$ SD results show that the fasting blood glucose level was notably changed (p<0.07) at the end of 6-month drug therapy. The data further reveals that the level of high-density lipoproteins in diabetic individuals rises again after the use of hypoglycemic agents (DPP–4 alone) for six months or more and the dissimilarity was outstanding (p<0.03). Similar findings were obtained for blood urea (p<0.07).

Table 1: General Characteristics and Various Demographic Parameters (Means$\pm$SD) of Study Subjects

Parameters	Group A (n=100)	Group B (n=100)	p-value
Age (Years)	52.50$\pm$11.80	59.00$\pm$15.70	0.002
BMI (Kg/m^2)	32.25$\pm$6.68	27.94$\pm$5.21	0.000
SBP (mmHg)	127.60$\pm$19.80	119.39$\pm$7.45	0.000
DBP (mmHg)	81.00$\pm$10.67	79.00$\pm$8.01	0.130
Pulse	90.00$\pm$2.80	85.00$\pm$9.52	0.000
Heart Rate	68.00$\pm$3.22	67.00$\pm$1.33	0.471

Values are given as mean +SD

Table 2: The Effect of Use of Dipeptidyl Peptidase–4 (DPP–4) Inhibitors alone on Biochemical Parameters (Group A)

Biochemical Parameter	Baseline	03 Months	p–values	6 Months	p–values
FBS (mg/dL)	189.33$\pm$82.95	142.67$\pm$47.86	0.26	113.33$\pm$40.86	0.07
RBS (mg/dL)	402.83$\pm$115.80	333.33$\pm$134.71	0.36	267.00$\pm$170.2	0.13
HbA1C	9.00$\pm$3.45	8.50$\pm$3.45	0.03	7.00$\pm$2.92	0.05
Lipid Profile					
Cholesterol (mg/dL)	211.67$\pm$38.68	182.50$\pm$19.42	0.13	147.50$\pm$81.59	0.11
Triglycerides (mg/dL)	205.33$\pm$148.41	135.00$\pm$62.53	0.31	129.00$\pm$70.48	0.28
HDL–c (mg/dL)	39.00$\pm$5.44	40.67$\pm$3.44	0.05	43.33$\pm$5.57	0.03
LDL–c (mg/dL)	127.26$\pm$32.96	121.50$\pm$17.37	0.49	90.05$\pm$69.61	0.17
Renal Profile					
Urea (mg/dL)	50.33$\pm$16.50	33.33$\pm$14.12	0.08	36.67$\pm$4.17	0.07
S. Creatinine (mg/dL)	1.35$\pm$0.50	1.18$\pm$0.39	0.50	1.00$\pm$0.154	0.12
Serum Electrolytes					
Na$^+$ (m mol/L)	138.00$\pm$5.65	136.00$\pm$0.00	0.40	139.33$\pm$4.50	0.66
K$^+$ (m mol/L)	4.41$\pm$0.57	3.75$\pm$1.66	0.37	4.28$\pm$0.57	0.69

Values are given as mean +SD

Table 3 represents the effects of the use of combination drugs (DPP–4 inhibitor (Sitagliptin 50 mg 1 BD) and metformin in a dose of 500 mg two times a day) on biochemical parameters of diabetic subjects from baseline to 6 months duration of treatment. Mean$\pm$SD fasting blood sugar of diabetic individuals at the start, at after three (03) and six (06) months were found to be 145.40$\pm$56.92, 125.40$\pm$35.63 and 100.40$\pm$22.80 mg/dL respectively and insignificant change in the result (p>0.05) was observed for at the end of three months. However, the difference was highly outstanding (p<0.001) in the case of RBS after 6 months of combination drug therapy. The mean$\pm$SD HbA1C at the start after three and six months of treatment was found to be 8.25$\pm$1.91, 7.50$\pm$1.65, and 6.00$\pm$1.46, and the change was significant (p<0.05). A highly significant change (p < 0.00) was observed for serum total cholesterol HDL–c and LDL–c after six months duration of treatment with DPP–4 and metformin it was non–significant change (p>0.05) for TG. Mean$\pm$SD of blood urea of diabetic individuals at the start and following three and six months therapies were 32.80$\pm$5.49, 28.20$\pm$4.26, and 27.50$\pm$5.75 mg/dL respectively and insignificant change (p > 0.05) was noted. Similarly, mean$\pm$SD of serum creatinine at baseline, three and six months therapies were 1.20$\pm$0.31, 1.12$\pm$0.39, and 0.86$\pm$0.25 mg/dL, and significant difference (p<0.05) was noted. Contrast

results were obtained in the case of serum electrolytes especially serum potassium levels in the instant study.

Table 3: The Effect of Use of Combination Drugs (Dipeptidyl Peptidase–4 Inhibitors + Metformin) (Group B)

Biochemical Parameter	Baseline	03 Months	p–values	6 Months	p–values
FBS (mg/dL)	145.40+56.92	125.40+35.63	0.35	100.40+22.80	0.03
RBS (mg/dL)	308.30+75.50	249.80+66.03	0.08	186.50+66.51	0.00
Hb A1c	8.25+1.91	7.50+1.65	0.55	6.00+1.46	0.019
Lipid Profile					
S. Total Cholesterol (mg/dL)	202.00+30.11	180.00+28.75	0.91	130.00+29.48	0.00
Triglyceride (mg/dL)	143.50+27.29	136.50+46.55	0.68	111.00+25.14	0.01
HDL–c (mg/dL)	38.40+6.51	43.70+6.21	0.07	44.80+4.89	0.04
LDL–c (mg/dL)	129.60+28.11	134.90+27.81	0.67	102.00+24.01	0.00
Renal Profile					
Urea (mg/dL)	32.80+5.49	28.20+4.26	0.05	27.50+5.75	1.00
S. Creatinine (mg/dL)	01.20+0.31	01.12+0.39	0.61	0.86+0.25	0.01
Serum Electrolytes					
Na$^+$ (m mol/L)	135.70+1.56	137.80+2.89	0.05	138.90+3.63	0.02
K$^+$ (m mol/L)	04.40+0.44	04.29+0.51	0.61	04.30+0.56	0.66

Values are given as mean +SD

Discussion

Dipeptidyl peptidase–4 inhibition decreases glucose levels and enhances beta cells' function and decreases glucagon level, increased intact glucagon-like–peptide–1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP). DPP–4 inhibitors control hyperglycemia in type–2 diabetes by affecting fasting as well as postprandial glucose.[25] The results of our study are congruous with the studies mentioned above. Verities of DPP–4 inhibitors exist[26], and they decrease the HbA1C by ≈ 5–10 mmol/L in dual therapy (when added to metformin) and in monotherapy in studies over 6 months. Better glycemic control is attained by inactivation of the DPP4 enzyme that inhibits incretin hormones (GLP-1 and GIP).[27] DPP–4 inhibition decreases glycemia sustainably. Furthermore, the reduction in glucagon after DPP–4 inhibition illustrated the chief mechanism supporting the improvement in glycaemia[28]. The DPP–4 inhibitor varies in its structure and enzyme binding characters and pharmacokinetics. The effectiveness degree of DPP–4 inhibition varies between DPP–4 inhibitors however inhibition is sustained at 70 to 90% over 24 hours after drug administration.[28] DPP–4 inhibitor is comprised of various types i.e. Alogliptin that affects improving insulin resistance when used in dual therapy with another hypoglycemic agent.[29–31]

Dipeptidyl Peptidase–4 is a class of drugs that reduces the inactivation of GLP–1 and GIP which increases the synthesis of insulin and decreases glucagon release by pancreatic cells. Glycemic effectiveness is achieved when both DPP–4 and biguanide are used together. The same result was also noted by Sharma M *et al*., (2017)[32] and Jain R (2015)[33] respectively, and thus are in agreement with our results. Our observations regarding glycemic control by the use of DPP–4 as monotherapy was almost similar to that of sulfonylurea (as monotherapy) and is in accordance with the findings reported by Sharma M and coworkers (2017)[32] however they instead of monotherapy used dual therapy (DPP–4 and Biguanide) and our results regarding dual therapy (DPP–4+Sulfonylurea) are almost comparable with the above.

According to our research on hypoglycemic agents used up to six months in monotherapy most effective drugs are sulfonylurea followed by DPP–4 regarding the reduction in HbA1C however, the result was carried out by Amir. Q and coworkers (2017) on hypoglycemic control show that using sulfonylurea class drugs over DPP–4 reduces Hb A1C but it has contradictory with the results that biguanide falls on the second number as compared to DPP–4.[34] Effectiveness and protection of DPP–4 inhibitor combination treatment had been shown by numerous multicenter, non-specific, double-blind, placebo-controlled studies.[35] Alike prior studies that manifested that combination treatment of DPP–4 inhibitor was secure and effective, the current survey indicated that the risks of severe hypoglycemia and death in patients dosed roughly with DPP–4 inhibitor in dual therapy were not different from those obtained with proper dosing of DPP–4 inhibitor as

monotherapy.[36,37] To achieve much more effective results in controlling fasting and random blood glucose level and glycosylated hemoglobin we used combination therapy (dual therapy). Encouraging results were obtained in the case of dipeptidyl peptidase class along with sulfonylurea which reduces HbA1C concentration up to 2.25 from the results observed at baseline and the present results are in accordance with the observations reported by Amir Q and coworkers(2017).[34]

Conclusion

DPP–4 inhibition prevents hypoglycemia via increased glucagon counter-regulation through the incretin hormone glucose-dependent insulinotropic polypeptide. A combination of DPP–4 inhibitors with Biguanides has good glycemic control over DPP–4 inhibitors as monotherapy in obese T2DM with fewer chances of hypoglycemia.

References

1. WhO O. Preventing and managing the global epidemic. Report of a WHO consultation on obesity. Geneva: WHO. 1997 Jun 3:17-40.
2. Rehman G, Khan SA, Hamayun M. Studies on diabetic nephropathy and secondary diseases in type 2 diabetes. Int. J. Diab. Dev. Ctries. 2005;25:25-9.
3. Skyler JS, Bakris GL, Bonifacio E, Darsow T, Eckel RH, Groop L, et al. Differentiation of diabetes by pathophysiology, natural history, and prognosis. Diabetes. 2017 Feb 1;66(2):241-55. https://doi.org/10.2337/db16-0806
4. Saxena R, Hivert MF, Langenberg C, Tanaka T, Pankow JS, Vollenweider P,et al . Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge. Nature genetics. 2010 Feb;42(2):142-8.
5. Nauck MA. Incretin-based therapies for type 2 diabetes mellitus: properties, functions, and clinical implications. The American journal of medicine. 2011 Jan 1;124(1):S3-18. https://doi.org/10.1016/j.amjmed.2010.11.002
6. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini Peters AL, Tsapas A, et al. Management of hyperglycaemia in type 2 E, Nauck M, diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2012 Jun 1;55(6):1577-96.
7. Wang TJ, Larson MG, Vasan RS, Cheng S, Rhee EP, McCabe E, et al. Metabolite profiles and the risk of developing diabetes. Nature medicine. 2011 Apr;17(4):448-53.
8. Cowie CC, Rust KF, Byrd-Holt DD, Gregg EW, Ford ES, Geiss LS, et al. Prevalence of diabetes and high risk for diabetes using A1C criteria in the US population in 1988–2006. Diabetes care. 2010 Mar 1;33(3):562-8. https://doi.org/10.2337/dc09-1524
9. Saran, R.; Robinson, B. Abbott, K. C. Vahakn, S. John, A. Nickol. B et al. US Renal Data System 2019 Annual Data Report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2020; 75:S1–S64.
10. Monami M, Dicembrini I, Antenore A, Mannucci E. Dipeptidyl peptidase-4 inhibitors and bone fractures: a meta-analysis of randomized clinical trials. Diabetes care. 2011 Nov 1;34(11):2474-6. https://doi.org/10.2337/dc11-1099
11. Mulvihill EE, Drucker DJ. Pharmacology, physiology, and mechanisms of action of dipeptidyl peptidase-4 inhibitors. Endocrine reviews. 2014 Dec 1;35(6):992-1019. https://doi.org/10.1210/er.2014-1035
12. Lu G, Hu Y, Wang Q, Qi J, Gao F, Li Y, et al. Molecular basis of binding between novel human coronavirus MERS-CoV and its receptor CD26. Nature. 2013 Aug;500(7461):227-31.
13. Davidson J. The placement of DPP-4 inhibitors in clinical practice recommendations for the treatment of type 2 diabetes. Endocrine Practice. 2013 Nov 1;19(6):1050-61. https://doi.org/10.4158/EP12303.RA
14. Deacon CF, Holst JJ. Dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes: comparison, efficacy and safety. Expert opinion on pharmacotherapy. 2013 Oct 1;14(15):2047-58. https://doi.org/10.1517/14656566.2013.824966
15. Ussher JR, Drucker DJ. Cardiovascular biology of the incretin system. Endocrine reviews. 2012 Apr 1;33(2):187-215. https://doi.org/10.1210/er.2011-1052
16. Solun B, Marcoviciu D, Dicker D. Dipeptidyl peptidase-4 inhibitors and their effects on the cardiovascular system. Current cardiology reports. 2013 Aug 1;15(8):382.
17. Puepet FH, Zoakah AI, Chuhwak EK. Prevalence of overweight and obesity among urban Nigeria adults in Jos. Highland Medical Research Journal. 2002;1(1):13-6. DOI: 10.4314/hmrj.v1i1.33792
18. Puoane T, Fourie JM, Shapiro M, Rosling L, Tshaka NC, Oelefse A. 'Big is beautiful'–an exploration with urban black community health workers in a South African township. South African Journal of Clinical Nutrition. 2005 Apr 1;18(1):6-15. https://doi.org/10.1080/16070658.2005.11734033
19. Hanson RL, Imperatore G, Bennett PH, Knowler WC. Components of the "metabolic syndrome" and incidence of type 2 diabetes. Diabetes. 2002 Oct 1;51(10):3120-7. https://doi.org/10.2337/diabetes.51.10.3120
20. Baker JL, Olsen LW, Sørensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. New England journal of medicine. 2007 Dec 6;357(23):2329-37. DOI: 10.1056/NEJMoa072515
21. Abbas S, Shazia A, Riaz A, Malik N. Risk factors for coronary artery disease in. Pakistan. Pak Armed Forces Med J 2003; 53: 12-9. 21.
22. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US adults: the Third National Health and Nutrition Examination Survey, 1988–1994. Diabetes care. 1998 Apr 1;21(4):518-24. https://doi.org/10.2337/diacare.21.4.518
23. Scheen AJ. Cardiovascular effects of dipeptidyl peptidase-4 inhibitors: from risk factors to clinical outcomes. Postgraduate medicine. 2013 May 1;125(3):7-20. https://doi.org/10.3810/pgm.2013.05.2659
24. Ramirez, G. Morrison, A. D. Bittle, P. A. Clinical practice considerations and review of the literature for the use of DPP–4 inhibitors in patients with type 2 diabetes and chronic kidney disease. Endocr Pract. 2013; 1025–1034.
25. Drucker DJ, Yusta B. Physiology and pharmacology of the enteroendocrine hormone glucagon-like peptide-2. Annual review of physiology. 2014 Feb 10;76:561-83. https://doi.org/10.1146/annurev-physiol-021113-170317
26. Mentlein R, Gallwitz B, Schmidt WE. Dipeptidyl peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon like peptide 1 (7–36) amide, peptide histidine methionine and is responsible for their degradation in human serum. European

journal of biochemistry. 1993 Jun;214(3):829-35. https://doi.org/10.1111/j.1432-1033.1993.tb17986.x

27. Egan AG, Blind E, Dunder K, de Graeff PA, Hummer BT, Bourcier T, et al. Pancreatic safety of incretin-based drugs—FDA and EMA assessment. New England Journal of Medicine. 2014 Feb 27;370(9):794-7. DOI: 10.1056/NEJMp1314078

28. Ahrén BO, Simonsson E, Larsson H, Landin-Olsson M, Torgeirsson H, Jansson PA, et al. Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4-week study period in type 2 diabetes. Diabetes care. 2002 May 1;25(5):869-75. https://doi.org/10.2337/diacare.25.5.869

29. Nakamura K, Oe H, Kihara H, Shimada K, Fukuda S, Watanabe K, et al. DPP-4 inhibitor and alpha-glucosidase inhibitor equally improve endothelial function in patients with type 2 diabetes: EDGE study. Cardiovascular Diabetology. 2014 Dec;13(1):1-0.

30. Alsalim W, Göransson O, Tura A, Pacini G, Mari A, Ahrén B. Persistent whole day meal effects of three dipeptidyl peptidase⬜4 inhibitors on glycaemia and hormonal responses in metformin⬜treated type 2 diabetes. Diabetes, Obesity and Metabolism. 2020 Apr;22(4):590-8. https://doi.org/10.1111/dom.13934

31. Chehregosha H, Khamseh ME, Malek M, Hosseinpanah F, Ismail-Beigi F. A view beyond HbA1c: role of continuous glucose monitoring. Diabetes Therapy. 2019 Jun 1;10(3):853-63.

32. Sharma M, Beckley N, Nazareth I, Petersen I. Effectiveness of sitagliptin compared to sulfonylureas for type 2 diabetes mellitus inadequately controlled on metformin: a systematic review and meta-analysis. BMJ open. 2017 Oct 1;7(10):e017260. http://dx.doi.org/10.1136/bmjopen-2017-017260

33. Jain R. Utility of saxagliptin in the treatment of type 2 diabetes: review of efficacy and safety. Advances in therapy. 2015 Nov 1;32(11):1065-84.

34. Amir, Q. MichaeL, J.B. Linda, L. Humphrey, and Mary A. F. Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update from the American College of Physicians. Ann Intern Med. 2017; 166:279–290.

35. Hong S, Han K, Park CY. Outcomes for Inappropriate Renal Dose Adjustment of Dipeptidyl Peptidase-4 Inhibitors in Patients With Type 2 Diabetes Mellitus: Population-Based Study. InMayo Clinic Proceedings 2020 Jan 1 (Vol. 95, No. 1, pp. 101-112). Elsevier. https://doi.org/10.1016/j.mayocp.2019.06.010

36. Liu Z, Xu L, Xing M, Xu X, Wei J, Wang J, et al. Trelagliptin succinate: DPP-4 inhibitor to improve insulin resistance in adipocytes. Biomedicine & Pharmacotherapy. 2020 May 1;125:109952. https://doi.org/10.1016/j.biopha.2020.109952

37. Avogaro A, Delgado E, Lingvay I. When metformin is not enough: Pros and cons of SGLT2 and DPP⬜4 inhibitors as a second line therapy. Diabetes/metabolism research and reviews. 2018 May;34(4):e2981. https://doi.org/10.1002/dmrr.2981