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TREATMENT WITH GLIPTINS AND STUDY OF THE VARIATIONS IN SERUM AMYLASE AND SERUM LIPASE LEVELS IN TYPE 2 DIABETES MELLITUS

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Key words:

dipeptidyl peptidase-4 (DPP-4)inhibitor,serum amylase,serum lipase, pancreatic inflammation

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ABSTRACT: Objective: To observe the variations in levels of serum amylase and serum lipase, in patients with type 2 DM after treatment with DPP-4 inhibitors. METHODS: Under this study, 174 Type 2 diabetes mellitus patients were analysed for variations in levels of exocrine pancreatic enzymes after use of dipeptidyl peptidase (DPP) 4 inhibitors. The effect was compared with those under treatment with other oral hypoglycaemic agents. Cases included in the study (n=90) were patients of type 2 diabetes mellitus on gliptins ± other oral hypoglycemic drugs. The control (n=84) included age and sex matched subjects, treated with other antihyperglycemic agents other than gliptins. Serum amylase and serum lipase levels were monitored at baseline, 3monthly and 6 monthly intervals. **Results**: Mean serum amylase levels in cases as compared to controls at 3 and 6 monthly intervals were 61.38±14.35U/L;94.57 ± 22.99U/L and 43.34± 9.80U/Land 45.72 ±8.40 U/L respectively. Difference between two groups was statistically significant at both time intervals. Similarly mean serum lipase levels in cases as compared to controls at 3 and 6 monthly intervals were 78.43 ± 44.79U/L;126.59 ± 110.08U/Land 52.17 ± 6.9 U/Land 6.94 ± 15.22U/L respectively. The serum lipase values too demonstrated that the diference between two groups was statistically significant at both time intervals. **Conclusion**: Significant rise in pancreatic exocrine enzyme levels was observed after treatment with DPP4 inhibitors in Type2 diabetes mellitus patients. None of the patients presented with acute pancreatic inflammation, suggesting that these agents lead to an inflammatory effect in the exocrine pancreas not amounting to clinical expression of pancreatitis.

INTRODUCTION: DPP-4 inhibitors are a newer class of anti-diabetic agents with efficacy comparable to in-use treatment regimen. Glucoregulatory effects of incretins (Glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]) are the basis for these new drugs.[1-4] Drugsthat inhibit enzyme dipeptidyl peptidase-4 (DPP-4), increase the active levels of GLP-1 and GIP, and in doing so they improve the islet function and glycemic control in T2DM [5-11] Other beneficial effects are low risk of hypoglycemia and weight neutrality.[12-16]

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Gliptins have recently became a matter of controversy as their usage has lead to some reports of exocrine pancreatic insufficiency resulting in rise in serum amylase and serum lipase levels in patients. Some prospective studies done in this regard have also reported similar findings. Occurrence of acute pancreatitis in DPP 4 treated patients have been infrequent and rarely reported. However, as gliptins are widely accepted and prescribed in T2DM, this phenomenon is of great concern to both diabetologist and patients together. This prospective study is thus planned in the same reference to look into the occurrence of rise in serum amylase and lipase values following gliptin therapy and whether there could be some serious consequences related to this occurrence

MATERIALS AND METHODS: This prospective study was conducted in patients treated in diabetes clinic on OPD basis in Department of

Medicine, King George's Medical University, Lucknow, during year 2014-2015. Cases included in the study (n=90) were patients of type 2 diabetes mellitus (age >=30yr) treated with gliptins ± other oral hypoglycemic drugs. The controls (n=84) included subjects with matched characteristics and treated with other oral hypoglycaemic agents except gliptins. Serum amylase, serum lipase, fasting blood sugars, post prandial blood sugars and glycosylated haemoglobin (HbA1c) were moniterd at 3 monthly and 6 monthly intervals. Serum enzyme levels >3 times of the upper limit of normal were taken as the cut off value.

Patients were explained warning signs like abdominal discomfort, pain abdomen, nausea and vomiting and were asked to visit in OPD if such symptoms appeared. Three subgroups were created in the case group namely subgroup A(n=33), B(n=30) and C(n=27) being on sitagliptin, vildagliptin and linagliptin respectively, in equivalent doses. Intersubgroup variation with respect to the enzyme levels was also observed at 3 monthly intervals. We excluded patients with history of prior pancreatitis, patients on treatment with antimetabolites, chronic alcoholics, those with hypertriglyceridemia (>1000 mg/dl), cholelithiasis and post ERCP patients. Serum amylase and serum lipase levels were analysed by *Vitros 250* micro slide using dry chemistry analyzer colourimethod. All the other biochemical parameters observed in the study were analysed by Biochemistry Roche (COBAS C 311, Germany).

RESULTS:

The data hereunder has been analyzed under two simulations:

a) Case-Control Evaluation at Group Level

b) Case-Control Evaluation at Subgroup Level

Case-Control Evaluation at Group Level (**Table 1**)

TABLE 1: COMPARISON OF DEMOGRAPHIC PROFILE OF PATIENT

SN	Characteristic	Cases (n=90)		Controls (n=84)		Significance of difference	
1.	Mean Age±SD (Range) in years	51.01±7.93 (38-75)		50.07±9.72 (34-76)		t=0.510; p=0.476	
2.	Gender	No.	%	No.	%	χ^2	P
	Male	52	57.8	54	71.4	1.513	0.219
	Female	38	42.2	30	35.7		

In both the groups majority of patients were males. Though the proportion of males was higher in Controls (66.7%) as compared to Cases (57.8%) yet this difference was not significant statistically (p=0.219). (**Table 2)**

TABLE 2: COMPARISON OF S. AMYLASE LEVELS AT DIFFERENT FOLLOW UP INTERVALS IN CASES AND CONTROLS

SN	Time interval	Cases (n=90)		Controls (n=84)		Significance of difference	
		Mean	SD	Mean	SD	't'	'p'
1.	Baseline	42.68	6.68	43.71	8.25	-0.92	0.357
2.	3 months	61.38	14.35	43.34	9.80	9.85	<0.001
3.	6 months	94.57	22.99	45.72	8.40	18.93	<0.001

At baseline, mean S. amylase levels in Cases and Controls were 42.68±6.68 U/L and 43.71±8.25 U/L respectively, thus showing statistically no significant difference between two groups (p=0.557).

At 3 months follow up, mean S. amylase level in cases was 61.38±14.35 U/L as compared to 43.34±9.80 U/L in controls thus showing a significant difference between two groups (p<0.001).

At 6 months follow up, mean S. amylase level in cases was 94.57±22.99 U/L as compared to 45.72±8.40 U/L in controls thus showing a significant differe6ce between two groups (p<0.001). (**Fig. 1**)

At baseline, mean S. Lipase levels in Cases and Controls were 41.91±9.22 U/L and 44.73±11.75 U/L respectively, thus showing statistically no significant difference between two groups (p=0.075). (**Table 3**)

TABLE 3: COMPARISON OF S. LIPASE LEVELS AT DIFFERENT FOLLOW UP INTERVALS IN CASES AND CONTROLS

SN	Time interval	Cases (n=90)		Controls (n=84)		Significance of difference	
		Mean	SD	Mean	SD	't'	'p'
1.	Baseline	41.91	9.22	44.73	11.75	-1.79	0.075
2.	3 months	78.43	44.79	52.17	6.94	5.50	<0.001
3.	6 months	126.59	110.08	64.62	15.22	5.29	<0.001

At 3 months follow up, mean S. lipase level in cases was 78.43±44.79 U/L as compared to 52.17±6.94 U/L in controls thus showing a significant difference between two groups (p<0.001).

At 6 months follow up, mean S. lipase level in cases was 126.59±110.08 U/L as compared to 64.62±15.22 U/L in controls thus showing a significant difference between two groups (p<0.00) (**Fig. 2**)

For S. amylase and S. lipase, statistically no significant difference among control and different subgroups of cases was observed at baseline but at both the subsequent follow ups, the difference among control and different subgroups of cases was significant (p<0.001). (**Table 4; Fig. 3**)

TABLE 4: CASE-CONTROL EVALUATION AT SUB GROUP LEVEL

SN	Time interval	Control (n=90)		Cases						Signi-ficance of difference	
				Sub group A (n=33)		Sub group B (n=30)		Sub group C (n=27)			
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	P
						S. Amylase					
1.	Baseline	43.7	8.3	43.7	8.0	42.7	6.6	41.7	5.2	0.636	0.593
2.	3 months	43.3	9.8	65.4	15.9	59.5	11.9	59.3	14.6	34.44	<0.001
3.	6 months	45.7	8.4	104.1	26.1	90.9	21.9	88.8	17.8	133.0	<0.001
						S. Lipase					
1.	Baseline	44.7	11.8	39.9	8.4	40.8	8.8	45.0	9.9	2.42	0.068
2.	3 months	52.2	6.9	90.3	50.3	73.9	40.5	71.1	42.0	12.49	<0.001
3.	6 months	64.6	15.2	155.4	137.4	115.8	98.1	108.5	85.8	11.67	<0.001

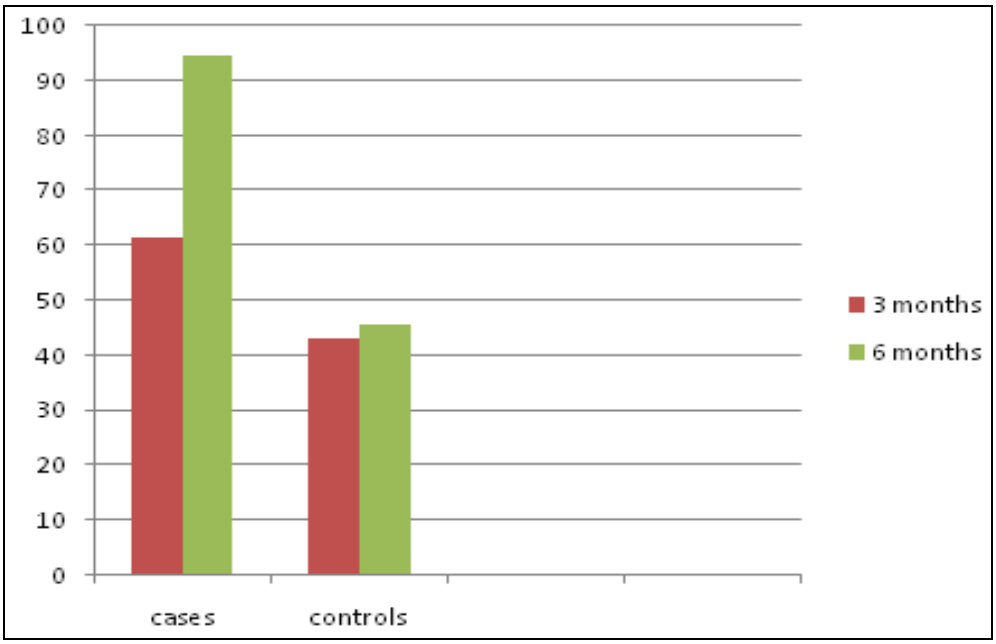

FIG. 1: OBSERVATION OF SERUM AMYLASE VALUES IN DIFFERENT GROUPS AT 3 MONTHLY AND 6 MONTHLY INTERVALS

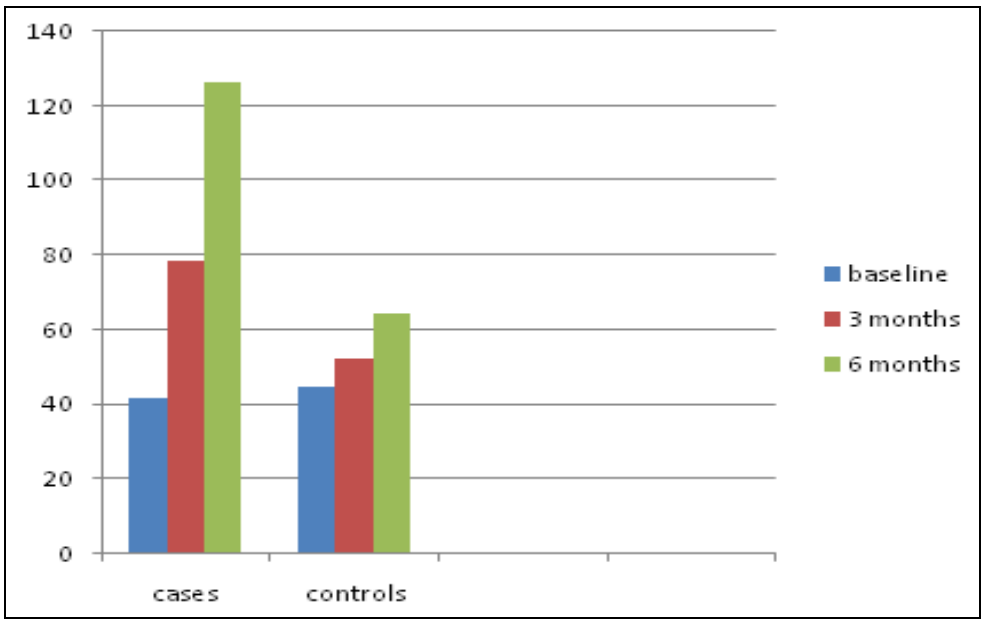

FIG.2: OBSERVATION OF SERUM LIPASE VALUES IN DIFFERENT GROUPS AT 3 MONTHLY AND 6 MONTHLY INTERVALS

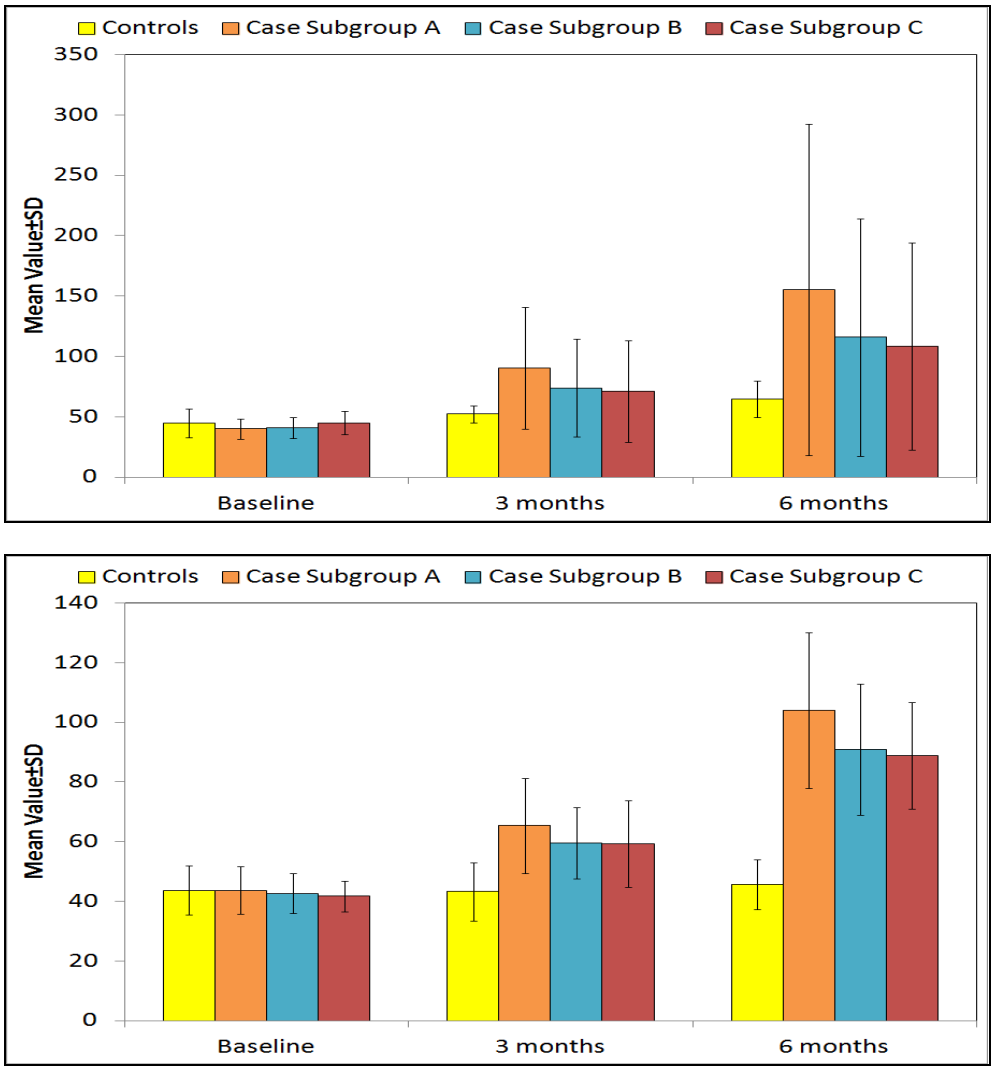

FIG.3: OBSERVATIONS OF SERUM AMYLASE AND SERUM LIPASE VALUES IN DIFFERENT SUBGROUPS AT 3 MONTHLY AND 6 MONTHLY INTERVALS.

For serum amylase, at 3 months, subgroups had significantly higher mean value as compared to control group; but no significant difference was observed between different subgroups of cases. At 6 months interestingly, mean value of subgroup A was significantly higher as compared to subgroups B and C but no significant difference was observed between subgroups B and C.

For serum lipase, statistically no significant differences between group were observed for any of the comparisons at baseline. However, at 3 and 6 months, the subgroups had significantly higher mean values as compared to the control group. There was no inter subgroup variation in relation to serum lipase values.

DISCUSSION: Recent reports of pancreatic exocrine insufficiency resulting from DPP-4inhibitor therapy has drawn worldwide attention. These drugs were widely accepted and prescribed presently and such reports are of utmost concern related to safety profile of these agents. Though this occurrence is not an uniform observation as some studies could not find the rise in pancreatic enzymes in study subjects on gliptin theray. In response to this controversial front ,we too wanted to observe this phenomenon on our patients of type 2 diabetes mellitus formulating this work as a prospectively study.

We included 174 diabetic patients in our study, 90 were kept on DPP4 inhibitors with or without any other oral hypoglycaemic drug and 84 were kept on oral hypoglycaemic drugs other than gliptins. Three subgroups were created i.e. A, B and C on the basis of the different gliptins prescribed i.e. Sitagliptin, Vidagliptin and Linagliptin respectively. The variation in level of exocrine pancreatic enzymes (serum amylase, serum lipase) after administration of these drugs was observed ay baseline, 3 months and 6 months.

Over 3 monthly intervals, the serum amylase levels had a slight rise over the first 3 months and a further rise over the next 3 months. Comparison of case with control group also showed significant difference between the outcome of both the groups at follow up. In case group the mean amylase level were raised from baseline(42.68 ± 6.68) to 61.38 ± 14.35 at 3 monthly follow up and to 94.57 ± 22.99 at six monthly follow up; while in the control group such significant rise was not observed. The values at baseline: 43.7 ± 8.25, at 3 months: 43.34 ± 9.80, at 6 months: 45.72 ± 8.40 were not statistically significant.

On observing the lipase levels, a minimal rise was seen in case groups initially at 3 months which further elevated over the next 3 months suggesting ongoing pancreatic inflammation. Mean lipase levels in case group were 41.91 ± 9.22 at baseline and increased to 78.43 ± 44.79 and 126.59± 110.08 at 3month and 6 months intervals respectively. The control group however could not show any such rise in the enzyme levels as the values at baseline: 44.73± 11.75, at 3 months: 52.17± 6.94, at 6 months: 64.62± 15.22 were not statistically significant.

As an effect for further evaluation, the case group was divided into subgroups A, B and C on the basis of the different gliptins prescribed i.e. Sitagliptin, Vidagliptin and Linagliptin respectively. Equivalent doses of all three gliptins were given to the subjects. The subgroups had significantly higher mean amylase value as compared to the control group at all time intervals. No significant difference was observed in mean S. amylase values among the different subgroups of cases at 3 monthly interval {subgroup A (*sitagliptin*) - 65.4±15.9; subgroup B (*vidagliptin*)-59.5±11.9; subgroup C (*linagliptin*)-59.3±14.6)}. At 6 months, the mean value of subgroup A (104.1±26.1) was significantly higher as compared to subgroups B (90.9±21.9) and C (88.8±17.8). No significant difference was observed between subgroups B and C.

At 3 months and 6 months interval, the subgroups had significant higher mean serum lipase values as compared to the controls. No significant difference was observed between different subgroups of cases (subgroup A-90.3±50.3; subgroup B-73.9±40.5; subgroup C-71.13±42.2) at studied time intervals. At 6 months, the mean value of serum lipase for subgroup A (155.4±137.4) was significantly higher as compared to subgroups B (115 ±98.1) and C (108.5 ±85.8).

Several studies have been done in past in this regard. Both prospective and retrospective studies were carried out, to evaluate the action of DPP4 inhibitors on pancreas. Lando et al [17] in their prospective work (n=123) studied that DPP-4 inhibitors are associated with increased levels of serum lipase or serum amylase in many patients with type 2 diabetes, possibly suggesting the presence of pancreatic inflammation. Among all 90 patients who received a GLP-1 receptor agonist or a DPP-4 inhibitor, 32 (36%) had an increase in serum amylase or lipase (or both) in comparison with 6 of 33 patients (18%) in the control group.

M Jayaraman et al (2013) [18] conducted an observational study with patients of type 2 DM receiving one of the gliptins (Sitagliptin, vildagliptin, or saxagliptin) for at least 1 month.Serum amylase test was done immediately at clinical presentation along with USG abdomen was performed. Asymptomatic elevation of serum amylase >3× upper limit of normal was noted in five patients (2.4 per 100 patient years), without any sonological evidence of pancreatitis and one patient (0.48 per 100 patient years) presented with mild acute pancreatitis which resolved in 8 days. The work thus supported the occurrence of gliptin induced pancreatic inflammation.

Another prospective study done by H.Tokuyama et al (2013) [19] studied the effect of DPP-4i in twenty four Japanese patients patients with type 2 diabetes taking DPP-4i with or without any additional oral hypoglycaemic drug. With 12 matched patients taking metformin. Pancreatic amylase and lipase activity was evaluated at 0 week, 8 weeks and 24 weeks after start of treatment. These enzymes were slightly but significantly increased, suggesting DPP-4i cause a low-grade inflammatory change in the exocrine pancreas.

Certain retrospective or cross sectional studies have also contributed in this matter of interest and concluded variably. Ellshoff et al (2011) [20] described the effect of sitagliptin and exenatide over exocrine pancreas. They examined the US Food and Drug Administration's database of reported adverse events for those subjects who pancreatic inflammation to substantiate the safety of these agents against their side effects. were associated with the dipeptidyl peptidase–4 inhibitor sitagliptin and the glucagon-like peptide-1 mimetic exenatide, from 2004–2009. Observations concluded that the use of these drugs increased the odds ratio for pancreatitis 6 fold as compared to other therapies. ($P < 2 \times 10^{-16}$).

Garg R et al(2010) [21] in there retrospective work studied a large medical and pharmacy claims database where data for 7,86,656 patients was analyzed . Risk of acute pancreatitis was similar in the exenatide versus diabetic control group (0.9 [0.6–1.5]) and sitagliptin versus diabetic control group (1.0 [0.7–1.3]). Thus they could not find an association between the use of exenatide or sitagliptin and acute pancreatitis. Yet this observational cohort study could not exclude the possibility of an increased risk for pancreatic injury by GLP1 based therapies. A large population based cohort study (n=20,748) done by Fallie JL et al [22] (2014) to determine association of incretin based drugs with acute pancreatic inflammation concluded that the use of incretin based drugs was not associated with an increased risk of acute pancreatitis. Giorda B C et al(2014) aimed to compare the occurrence of acute pancreatitis in a population of patients with type 2 diabetes who received incretins compared with those who received other antidiabetic treatment. They extracted information from an administrative database whereby, 1003 out of 2 82 429 cases (older than 41 years) had been admitted to hospital for acute pancreatitis between Jan 1, 2008, and Dec 31, 2012.Interpretation of the observation was that use of incretins is not associated with an increased risk of acute pancreatitis. Present study carried prospectively, too demonstrated exocrine pancreatic inflammation occurring after gliptins use not amounting to acute pancreatitis.

CONCLUSION: The work observed pancreatic inflammation occurring after gliptins use in type 2 diabetes mellitus patients. The phenomenon was seen happening with different DPP4 inhibitors individually. None of the patients developed acute pancreatitis. More information is needed to establish cut off level of dose and duration of gliptins intake and the ways of evaluating

CONFLICT OF INTEREST: None

REFERENCES:

1. Singh AK. Dipeptidyl peptidase-4 inhibitors: Novel mechanism of actions. Indian J Endocrinol Metab. 2014 Nov-Dec; 18(6): 753–759.
2. Drucker DJ. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006 Nov 11; 368(9548):1696-705.
3. Meier JJ. New concepts in the treatment of type 2 diabetes. Internist (Berl). 2007 Jul; 48(7):698, 700-7.
4. Kleefstra N. New blood glucose-lowering drugs in type 2 diabetes: a review of the literature.2010; 154:A886.
5. Kathleen Dungan Glucagon-Like Peptide 1-Based Therapies for Type 2 Diabetes: A Focus on Exenatide. Clinical Diabetes *April 2005 vol. 23 no. 2 56-62*
6. Uccellatore A. Comparison Review of Short-Acting and Long-Acting Glucagon-like Peptide-1 Receptor Agonists. Diabetes Ther. 2015 Sep; 6(3): 239–256
7. Madsbad S.A review of head-to-head comparisons of GLP-1 receptor agonists. Diabetes Obes Metab. 2015 Oct 29
8. Gupta V, Kalra S Choosing a Gliptin Indian J Endocrinol Metab. 2011 Oct-Dec; 15(4): 298–308.
9. Yabe D, Seino Y. Two incretin hormones GLP-1 and GIP: comparison of their actions in insulin secretion and β cell preservation. Prog Biophys Mol Biol. 2011 Nov; 107(2):248-56
10. Seino Y, Yabe D Glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1: Incretin actions beyond the pancreas. J Diabetes Investig. 2013 Mar 18;4(2):108-30
11. Seino Y, Fukushima M. GIP and GLP-1, the two incretin hormones: Similarities and differences. J Diabetes Investig. 2010 Apr 22; 1(1-2):8-23.
12. Reid T. Choosing GLP-1 Receptor Agonists or DPP-4 Inhibitors: Weighing the Clinical Trial Evidence. Clinical Diabetes January 2012 vol. 30 no. 1 3-126
13. Morales J .The pharmacologic basis for clinical differences among GLP-1 receptor agonists and DPP4 inhibitors. Poastgrad Med.2011 nov;123(6):189-201
14. Neumiller J J. Dipeptidyl peptidase -4 inhibitors for the treatment of type2 diabetes mellitus. Pharmacotherapy. 2010 may; 30(5):463-84
15. James E Foley. Weight neutrality with the DPP-4 inhibitor, vildagliptin: Mechanistic basis and clinical experience. Vasc Health Risk Manag. 2010; 6: 541–548.
16. B. Ahren. Mechanisms of action of the dipeptidyl peptidase-4 inhibitor vildagliptin in humans. Diabetes, Obesity and Metabolism. September 2011; 13(9):775–783
17. Howard Lando, May Alattar Elevated Amylase and Lipase Levels in Patients Using Glucagonlike Peptide-1 Receptor Agonists or Dipeptidyl-Peptidase-4 Inhibitors in the Outpatient Setting
18. Muthukrishnan Jayaraman Acute pancreatitis with gliptins: Is it a clinical reality? Indian J Endocrinol Metab. 2013 Oct; 17(Suppl1): S323–S325.
19. Hirotake Tokuyama A low-grade increase of serum pancreatic exocrine enzyme levels by dipeptidyl peptidase-4 inhibitor in patients with type 2 diabetes .Diabetes Research and Clinical Practice, 2013; 100(3):e66-e69.
20. Elashoff M et al Pancreatitis, Pancreatic, and Thyroid Cancer with Glucagon-Like Peptide-1–Based Therapies Gastroenterology. 2011 Jul; 141(1): 150–156.
21. Garg R. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. Diabetes Care. 2010 Nov; 33(11):2349-54.
22. Jean-Luc Faillie Incretin based drugs and risk of acute pancreatitis in patients with type 2 diabetes: cohort study. BMJ. 2014; 348: g2780.

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