Brief Communication

Hyperamylasemia is not Associated with Dipeptidyl Peptidase 4 Inhibitors in South Indian Adults with Type 2 Diabetes Mellitus

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Abstract

Introduction: Although not definitive, there is small increased risk of acute pancreatitis with the use of dipeptidyl peptidase 4 inhibitors (DPP4i). Hence, there is an interest in the elevation of pancreatic enzymes among type 2 diabetes mellitus (T2DM) patients using DPP4i. However, the studies regarding their association are limited and provide conflicting results. Moreover, there are no such studies among South Indian T2DM patients. Hence, we evaluated the prevalence of hyperamylasemia among South Indian T2DM patients and its association with DPP4i use. **Methods:** This cross-sectional study was conducted at a tertiary health care center from South India. Adult T2DM patients on stable doses of antidiabetic medications for at least previous 3 months were included in the study. Patients with other types of diabetes mellitus, gall stones, diabetic ketoacidosis, acute illness, chronic kidney disease and untreated hypothyroidism were excluded from the study. All participants were evaluated with glycemic parameters, serum creatinine and serum amylase. Hyperamylasemia was defined as serum amylase ≥220 U/L. **Results:** A total of 200 participants were included in the study among whom 93 patients were not on DPP4i whereas 107 were on DPP4i including 41 (38.32%) each on teneligliptin and sitagliptin. Baseline characteristics including glycemic measures were comparable between DPP4i users and nonusers. A total of 14 patients (7%) had hyperamylasemia but the prevalence of hyperamylasemia did not differ between DPP4i users and nonuser (6/107 vs. 8/93, $P = 0.42$). **Conclusions:** Asymptomatic hyperamylasemia is not uncommon in South Indian T2DM patients but is not associated with the use of DPP4i.

Keywords: *Dipeptidyl peptidase 4 inhibitor, hyperamylasemia, south Indians, type 2 diabetes mellitus*

Introduction

Although not definitive, a recent meta-analysis has demonstrated a small increased risk of acute pancreatitis with the use of Dipeptidyl peptidase 4 inhibitors (DPP4i).[1] Hence, there is an interest in the elevation of pancreatic enzymes among type 2 diabetes mellitus (T2DM) patients using DPP4i. However, in patients treated with liraglutide, which is more frequently associated with elevated pancreatic enzymes in a dose-dependent manner, elevated pancreatic enzyme levels did not predict acute pancreatitis.[2] Nevertheless, several recent health-check packages for diabetic patients in India include serum amylase levels and often report an elevated level which poses a concern for the continuation of DPP4i in those T2DM patients (personal experience). Moreover, there is no data on the prevalence of hyperamylasemia and its association with DPP4i use among T2DM patients from South India. Hence, we evaluated the prevalence of hyperamylasemia among south Indian T2DM patients and its association with DPP4i use.

Methods

This cross-sectional study was conducted in the Department of Endocrinology, Narayana Medical College and Hospital, Nellore between August 2018 and January 2019. The study was approved by the institutional ethics committee and written informed consent was obtained from all the participants.

Assuming hyperamylasemia prevalence of 11% among DPP4i users and 3% among non-DPP4i users, an alpha error of 10%, and power of 0.8, a sample size of 93 in each group was estimated. We used consecutive sampling and recruited consecutive, eligible T2DM patients attending the endocrine outpatient care

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services until at least 93 participants in each group were included. This approach yielded 93 participants in DPP4i-nonuser group and 107 participants in DPP4i-user group. The choice of antidiabetic medications and doses were as per the discretion of the treating Endocrinologist, as part of the routine diabetes care.

T2DM patients of either sex, aged more than 18 years and on at least one antidiabetic medication with no change in the dose of antidiabetic medications at least during the last 3 months were included in the study. Patients with other types of diabetes mellitus, gall stones, diabetic ketoacidosis, acute illness, chronic kidney disease, untreated hypothyroidism and those on less than the maximum recommended doses of DPP4i were excluded from the study. Clinical data were collected using a prestructured pro forma and all participants underwent fasting plasma glucose, postprandial plasma glucose, serum creatinine, serum thyroid-stimulating hormone, and serum amylase.

Serum amylase level was measured by ethylidene blocked PNP-G7 colorimetric method using a fully automated clinical chemistry RX IMOLA analyzer by Randox Laboratories Ltd, County Antrim, UK. Serum amylase of more than 220 U/L was defined as hyperamylasemia as recommended by the manufacturer. The data was analyzed using SPSS 22.0 version, IBM, Corp., Armonk, NY, USA. Continuous variables were represented as mean ± standard deviation whereas categorical variables were represented as percentages. Unpaired *t*-test was used to compare the continuous variables between the two groups whereas the Chi-square test or Fischer exact *t*-test was used to compare categorical variables between the two groups as appropriate. A $P < 0.05$ was considered statistically significant.

Results

Out of the 200 participants 107 were on DPP4i. Sitagliptin and teneligliptin were received by 41 (38.3%) each, vildagliptin by 23 (21.5%), and linagliptin by 2 (1.9%). Hyperamylasemia was observed in 14 (7%) participants. Serum amylase level (115.14 ± 64.98 vs. 131.09 ± 83.26, $P = 0.13$) and prevalence of hyperamylasemia (6/107 vs. 8/93; $P = 0.42$) were not different between DPP4i users and DPP4i nonusers [Table 1]. Serum amylase levels among teneligliptin users (117.24 ± 74.02. $P = 0.36$) and sitagliptin users (108.07 ± 50.21. $P = 0.1$) and other DPP4i users were not significantly different. There were no significant differences in age, anthropometric parameters, glycemic parameters, and other common antidiabetic and antihypertensive drugs used between patients with normal and elevated serum amylase levels [Table 2].

Discussion

We report a high prevalence (7%) of asymptomatic hyperamylasemia among patients with T2DM. A large, international study has also reported elevated serum amylase levels in 7.7% of T2DM patients with normal renal function which is consistent with our study observations.[3] Serum amylase values more than 1000 U/L indicate pancreatitis whereas those between 300 and 1000 U/L indicate other conditions such as peptic ulcer disease, mesenteric ischemia, cholecystitis, intestinal obstruction, renal failure, and diabetic ketoacidosis. In our study, none of the patients had a serum amylase level of more than 1000 U/L, and all those who had elevated serum amylase were also asymptomatic for abdominal complaints which suggests against any of the above-listed abdominal conditions.[4] This may suggest the possibility of benign etiology for hyperamylasemia such as macroamylasemia in our study population. A few studies have also demonstrated the negative correlation of serum amylase levels with fasting plasma glucose and the duration of diabetes and a positive correlation with serum insulin levels.[5-7] Insulin treatment has been shown to increase pancreatic amylase activity. These observations may suggest insulin deficiency as the cause of elevated serum amylase in patients with diabetes mellitus. However, no such associations were found in our study.

A recent systematic review has demonstrated lower serum amylase levels in T2DM patients and metabolic syndrome subjects than in healthy controls.[8] Although the association of serum lipase levels with T2DM is variable, the association of low serum amylase levels with T2DM patients has been consistently reported by all Indian studies.[6,7,9] However, we have not compared the serum amylase level of our T2DM patients with those of healthy controls.

In contrast, a study from India demonstrated an increase in serum amylase levels after treatment initiation with DPP4i,[10] whereas another small study from Turkey has demonstrated such risk only with the use of sitagliptin but not with the use of saxagliptin or vildagliptin.[11] A prospective randomized controlled study with frequent monitoring of serum amylase levels demonstrated an increase in serum amylase 2 and 6 weeks after sitagliptin use which was normalized by week 12.[12] As all our patients were on DPP4i for more than 3 months, the change in serum amylase after drug initiation could not be evaluated and transient serum amylase elevation during the first few weeks of therapy might have been missed in our patients. Interestingly, the use of omarigliptin, a once-weekly DPP4i, was associated with mild but persistent elevation of serum amylase levels, though none of the patients had an elevation of serum amylase above the upper limit of normal.[13] However, whether this persistent elevation in serum amylase levels is related to the long-acting nature of the drug needs further evaluation.

The study was limited by the small sample size. Secondly, our study does not evaluate the prevalence of

Table 1: Comparison of characteristics of dipeptidyl peptidase-4 inhibitors users and dipeptidyl peptidase-4 inhibitors nonusers

Characteristics	DPP4i users (*n*=107), *n* (%)	DPP4i nonusers (*n*=93), *n* (%)	*P*
Age (years)	54.05±10.59	51.50±12.73	0.129
Height (cm)	160.01±7.38	162.87±6.66	0.004
Weight (kg)	68.30±11.33	66.95±11.32	0.401
Duration of DM (years)	7.08±4.77	5.65±6.08	0.069
Fasting plasma glucose (mg/dL)	150.47±56.23	143.02±56.53	0.353
Postprandial plasma glucose (mg/dL)	209.78±68.04	207.85±68.81	0.843
Serum amylase (U/L)	115.14±64.98	131.09±83.26	0.13
Prevalence of hyperamylasemia	6/107 (5.6)	8/93 (8.6)	0.42
Metformin	88 (82.2)	78 (83.8)	0.85
Sulfonylurea	48 (44.9)	52 (55.9)	0.09
Alpha glucosidase inhibitors	25 (23.4)	23 (24.7)	0.87
SGLT2 inhibitors	22 (20.2)	24 (25.8)	0.4
Insulin	20 (19.4)	19 (21.4)	0.85
Calcium channel blockers	17 (15.6)	14 (14.2)	0.99
Angiotensin receptor blockers	23 (21.5)	20 (21.4)	0.99
Diuretics	9 (9.1)	11 (21.4)	0.48

DPP4i: Dipeptidyl peptidase-4 inhibitors; DM: Diabetes mellitus; SGLT2: Sodium-glucose co-transporter-2

Table 2: Comparison of characteristics between patients with elevated and normal serum amylase levels

Characteristics	Normal serum amylase (*n*=186), *n* (%)	Hyperamylasemia (*n*=14), *n* (%)	*P*
Age (years)	53.04±11.59	50.64±12.93	0.459
Height (cm)	161.34±7.26	161.29±6.378	0.98
Weight (kg)	67.62±11.52	68.50±8.47	0.779
BMI (kg/m^2)	25.99±4.31	26.33±2.99	0.77
Duration of diabetes (years)	6.26±5.38	8.5±6.11	0.13
Fasting plasma glucose (mg/dL)	145.44±54.29	127.14±29.99	0.2146
Postprandial plasma glucose	210.24±68.80	190.79±59.50	0.3
Serum amylase (U/L)	108.23±46.88	312.93±105.91	0.0001
Males	86 (46.2)	6 (42.9)	0.81
Metformin	156 (85.7)	10 (71.4)	0.4
Sulfonylurea	92 (49.5)	8 (57.1)	0.78
Alpha glucosidase inhibitors	45 (24.2)	3 (21.4)	0.81
SGLT2 inhibitors	42 (22.6)	4 (28.6)	0.74
Insulin	36 (19.4)	3 (21.4)	0.85
Calcium channel blockers	29 (15.6)	2 (14.2)	0.9
Angiotensin receptor blockers	40 (21.5)	3 (21.4)	0.99
Diuretics	17 (9.1)	3 (21.4)	0.31

SGLT2: Sodium-glucose co-transporter-2; BMI: Body mass index

hyperamylasemia among the nondiabetic South Indians. Thirdly, serum lipase or pancreatic isoamylase which are more specific indicators of pancreatitis were not evaluated in our study. Finally, the study did not evaluate the reversibility of serum amylase elevation after withdrawing DPP4i which has been described in liraglutide users.[14] However, our study may not merit such an evaluation as there was no association between hyperamylasemia and DPP4i use.

Conclusions

Asymptomatic hyperamylasemia is not uncommon in South Indian patients with T2DM but is not associated with the use of DPP4i. Nevertheless, use of DPP4i should be avoided in patients with history of pancreatitis. Larger prospective studies are required to further evaluate the effect of various DPP4i on pancreatic enzyme levels and the risk of pancreatitis.

Ethical statement

The study was approved by the institutional ethics committee of Narayana Medical College (NMC/Adm/Ethics/approval/004/05/2018).

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Conflicts of interest

There are no conflicts of interest.

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