The Relationship Between Dipeptidyl Peptidase-4 Inhibitor Usage and Asymptomatic Amylase Lipase Increment in Type 2 Diabetes Mellitus Patients

Tip 2 Diabetes Mellitus Tanılı Hastalarda Dipeptidil Peptidaz-4 İnhibitör Kullanımı ile Asemptomatik Amilaz Lipaz Artışı Arasındaki İlişki

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ABSTRACT

Objectives: In different studies, it has been shown that the use of dipeptidyl peptidase-4 (DPP-4) inhibitors (DPP-4 inh) does not increase the risk of pancreatitis or pancreatic cancer. Although the number of studies involving clinical pancreatitis clinics is sufficient, the number of studies involving clinical non-pancreatitis hyperamylasemia is rare. The aim of the study was to investigate the relationship between DPP-4 inh usage and amylase and lipase increment without clinical pancreatitis symptoms.

Materials and Methods: Eighty-seven patients who met the inclusion criteria were enrolled. The patients were divided into 3 groups according to their use of saxagliptin, sitagliptin, or vildagliptin. All patients included in the study were receiving metformin at a dose of 2 g/day. Fasting blood glucose, postprandial blood glucose, HbA1C, serum creatinine, ALT, amylase, and lipase results were recorded at the beginning of treatment and at the end of 3 months.

Results: There was an increase in all groups in terms of amylase and lipase values but there was no significant difference between the groups in terms of increase (p>0.05). There was no statistically significant increase in the saxagliptin and vildagliptin groups (p>0.05) when the baseline and 3-month values of lipase and amylase increase were examined. However, there was a statistically significant increase in amylase and lipase in the sitagliptin group (p<0.05).

Conclusion: The use of DPP-4 inh can increase amylase and lipase levels without clinical findings of acute pancreatitis in the patient. DPP-4 inh should be used with caution in patients at risk for pancreatitis and pancreatic cancer. Patients using DPP-4 inh, especially sitagliptin, should be evaluated carefully for pancreatitis risk factors.

Key words: Oral antidiabetics, dipeptidyl peptidase-4 inhibitors, amylase, lipase
INTRODUCTION

Dipeptidyl peptidase 4 (DPP-4), an aminopeptidase that was isolated from the rat liver in 1960, is excreted in the pancreas, brain, lungs, kidneys, intestines, adrenal glands, and lymph nodes. Moreover, this enzyme causes glucagon-like peptide-1 (GLP-1) to break down in less than 2 min and gastric inhibitory polypeptide in less than 5 to 7 min. Dipeptidyl peptidase-4 inhibitors (DPP-4 inh) are oral antidiabetic agents that increase circulating GLP-1 levels. Thus, they help to inhibit the rapid inactivation of GLP-1 and regulate blood sugar. In other words, they control blood glucose by stimulating insulin secretion in glucose-dependent pathways. Although DPP-4 contains a wide range of substrates including chemokines, hormones, and neuropeptides, DPP-4 inh usually do not negatively affect type 2 diabetes (T2DM) patients. Several studies have evaluated the safety of DPP-4 inh in elderly patients as well as patients with renal insufficiency, liver disease, and/or heart failure. While most observational studies have demonstrated the safety of these inhibitors, they have nevertheless been associated with a slightly increased incidence of acute pancreatitis during placebo-controlled trials. In addition, the possible side effects of long-term DPP-4 inh use remain unclear. Those side effects observed during the preclinical and clinical trials of sitagliptin and vildagliptin treatments are inconsistent with the increased risk of pancreatitis in T2DM patients, but the association between DPP-4 inh and pancreatic cancer, pancreatitis, and pancreatic enzyme elevation has been proven. The Food and Drug Administration (FDA) has also reported that patients using sitagliptin and exenatide should be cautious in terms of developing pancreatic cancer. On the other hand, various studies have demonstrated that the use of DPP-4 inh does not increase the risk of pancreatitis or pancreatic cancer. Finally, although the number of studies involving pancreatic cancer patients is sufficient, those concerning patients with clinical non-pancreatic hyperamylasemia are rare. The present study assessed changes in the amylase and lipase values of various patients who had been using DPP-4 inh but did not exhibit acute pancreatitis symptoms.

MATERIALS AND METHODS

The participants were diabetic patients who had been referred to the endocrinology and metabolism clinic of Gaziantep Şahinbey research and application hospital. Prior to the study approval (approval no. 17/10/2016/268) was obtained from the Gaziantep University Committee. The study was prospective in nature, with patients being evaluated twice over a 3-month period (i.e. at 0 and 3 months). In addition, it was descriptive in nature and assessed the relationship among variables. All patients involved in this study met the following inclusion criteria developed by the American Diabetes Association:

1. Patients with T2DM
2. Patients who were not using antidiabetic drugs other than metformin and previously had not used sitagliptin, saxagliptin, or vildagliptin
3. Patients with HbA1C level lower than 10
4. Patients without cholelithiasis,
5. Patients without chronic alcohol consumption,
6. Patients with triglyceride levels lower than 150 mg/dL,
7. Patients in whom blood sugar regulation could not be achieved with metformin or any form of sitagliptin, saxagliptin, or vildagliptin treatment,
8. Patients without pancreatitis or pancreatitis history,
9. Patients with no history of renal or hepatic disease,
10. Patients without acute malignancy or malignancy history
11. Patients who were not pregnant,
12. Patients with no history of smoking or tobacco use,
13. Patients with no history of any type of cancer,
14. Patients with no history of any type of diabetes mellitus,
15. Patients with no history of any type of gastrointestinal disorder,
16. Patients with no history of any type of autoimmune disorder,
17. Patients with no history of any type of endocrine disorder,
18. Patients with no history of any type of thyroid disorder,
19. Patients with no history of any type of hepatic disorder,
20. Patients with no history of any type of renal disorder,
21. Patients with no history of any type of cardiac disorder,
22. Patients with no history of any type of pulmonary disorder,
23. Patients with no history of any type of neurological disorder,
24. Patients with no history of any type of psychological disorder,
25. Patients with no history of any type of psychiatric disorder,
26. Patients with no history of any type of behavioral disorder,
27. Patients with no history of any type of drug or alcohol abuse,
28. Patients with no history of any type of substance abuse,
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The 87 patients who met the above criteria were divided into 3 groups according to their use of saxagliptin, sitagliptin, or vildagliptin. All had been taking metformin at a dosage of 2 g/day at the start of the study. Patients using saxagliptin had been taking 1 mg of 5 mg daily, patients using sitagliptin had been taking 100 mg daily, and patients using vildagliptin had been taking 50 mg daily (morning and evening). Prior to and following the 3-month treatment, patients’ fasting blood glucose, postprandial blood glucose, hemoglobin A1c (HbA1c), serum creatinine, alanine transaminase (ALT), amylase, and lipase levels were recorded.

Statistical analysis

A minimum of 80 patients were required for the present study based on the results of power analysis conducted for sample selection. The normal distribution fitness of numerical data was tested using the Shapiro-Wilk test, while the Kruskal-Wallis test was used to compare normal nondispersive variables. The relationship among normally undistracted dependent variables was tested via the Wilcoxon test, and the relationship among categorical variables was tested using the chi-square test. SPSS 22.0 was employed for results analysis and a p-value < 0.05 was considered significant.

RESULTS

There was no statistically significant difference among the groups in terms of age or sex (p>0.05). The demographic characteristics of each group of participants are shown in Table 1.

At the beginning of the study, no significant difference in baseline fasting glucose level or postprandial blood glucose, HbA1C, serum creatinine, ALT, amylase, or lipase was observed (p>0.05) (Table 2). A statistically significant decrease in all groups (p>0.05) was found in fasting blood glucose, postprandial blood glucose, and HbA1C values after the 3-month treatment. Moreover, amylase and lipase values increased in all groups.

| n   | Saxagliptin | Sitagliptin | Vildagliptin | p   |
|-----|-------------|-------------|--------------|-----|
| Sex | 21/6        | 7/23        | 12/18        | 0.241|
| Age (year) | 54.26±7.906 | 56.33±6.572 | 54.00±10.316 | 0.577|
but there was no significant difference in these values when comparing the groups (p>0.05) (Table 3). By the end of the study, there was a statistically significant decrease in fasting blood glucose and HbA1C in all groups (p<0.05). However, in comparing the groups, the decline rates did not significantly differ. There was no statistically significant increase in lipase or amylase levels within the saxagliptin and vildagliptin groups (p>0.05) after the 3-month treatment. However, there was a statistically significant increase in amylase and lipase levels within the sitagliptin group (p<0.05). There was no statistically significant increase in ALT levels within the sitagliptin or vildagliptin groups (p>0.05), yet there was a statistically significant increase in ALT level within the saxagliptin group (p<0.05) (Table 4).

**DISCUSSION**

Sitagliptin, which has been used since 2006, is the longest of the DPP-4 inh in use; thus, more information is available regarding its use compared to other DPP-4 inh. According to the FDA’s reported side effect database, patients using sitagliptin or exenatide are more prone to develop pancreatic cancer than

### Table 2. Comparison of laboratory parameters of the groups at the beginning of treatment

| Parameter            | Group       | N  | Mean     | Std. deviation | p   |
|----------------------|-------------|----|----------|----------------|-----|
| Fasting glucose (mg/dL) | Saxagliptin | 27 | 204.41   | 69.841         |     |
|                      | Sitagliptin | 30 | 190.67   | 66.093         | 0.704|
|                      | Vildagliptin| 30 | 215.73   | 91.480         |     |
|                      | Total       | 87 | 203.57   | 76.679         |     |
| Postprandial glucose (mg/dL) | Saxagliptin | 27 | 344.30   | 112.314        | 0.621|
|                      | Sitagliptin | 30 | 275.97   | 114.564        |     |
|                      | Vildagliptin| 30 | 327.90   | 126.681        |     |
|                      | Total       | 87 | 315.08   | 120.458        |     |
| HbA1C (%)            | Saxagliptin | 27 | 9.41     | 2.005          | 0.700|
|                      | Sitagliptin | 30 | 8.97     | 1.650          |     |
|                      | Vildagliptin| 30 | 9.27     | 1.874          |     |
|                      | Total       | 87 | 9.21     | 1.831          |     |
| Creatinine (mg/dL)   | Saxagliptin | 27 | 0.93     | 0.267          | 0.885|
|                      | Sitagliptin | 30 | 0.90     | 0.305          |     |
|                      | Vildagliptin| 30 | 0.93     | 0.254          |     |
|                      | Total       | 87 | 0.92     | 0.274          |     |
| ALT (U/L)            | Saxagliptin | 27 | 23.07    | 10.954         | 0.905|
|                      | Sitagliptin | 30 | 24.57    | 10.448         |     |
|                      | Vildagliptin| 30 | 22.63    | 9.368          |     |
|                      | Total       | 87 | 23.44    | 10.168         |     |
| Amylase (U/L)        | Saxagliptin | 27 | 60.74    | 21.506         | 0.792|
|                      | Sitagliptin | 30 | 56.77    | 22.660         |     |
|                      | Vildagliptin| 30 | 56.03    | 21.714         |     |
|                      | Total       | 87 | 57.75    | 21.821         |     |
| Lipase (U/L)         | Saxagliptin | 27 | 19.65    | 12.776         | 0.394|
|                      | Sitagliptin | 30 | 25.32    | 17.035         |     |
|                      | Vildagliptin| 30 | 21.82    | 14.274         |     |
|                      | Total       | 87 | 22.35    | 15.297         |     |

HbA1C: Hemoglobin A1c, ALT: Alanine transaminase, Std: Standard

### Table 3. Laboratory parameters of the groups by the end of treatment

| Parameter            | Group       | N  | Mean     | Std. deviation | p   |
|----------------------|-------------|----|----------|----------------|-----|
| Fasting glucose (mg/dL) | Saxagliptin | 27 | 155.48   | 49.431         | 0.171|
|                      | Sitagliptin | 30 | 162.67   | 52.948         |     |
|                      | Vildagliptin| 30 | 182.37   | 61.222         |     |
|                      | Total       | 87 | 167.23   | 55.484         |     |
| Postprandial glucose (mg/dL) | Saxagliptin | 27 | 277.67   | 99.458         | 0.402|
|                      | Sitagliptin | 30 | 251.73   | 108.690        |     |
|                      | Vildagliptin| 30 | 271.97   | 109.553        |     |
|                      | Total       | 87 | 266.76   | 105.579        |     |
| HbA1C (%)            | Saxagliptin | 27 | 8.11     | 1.450          | 0.154|
|                      | Sitagliptin | 30 | 7.80     | 1.375          |     |
|                      | Vildagliptin| 30 | 8.57     | 1.569          |     |
|                      | Total       | 87 | 8.16     | 1.485          |     |
| Creatinine (mg/dL)   | Saxagliptin | 27 | 0.96     | 0.192          | 0.800|
|                      | Sitagliptin | 30 | 0.93     | 0.254          |     |
|                      | Vildagliptin| 30 | 0.97     | 0.183          |     |
|                      | Total       | 87 | 0.95     | 0.211          |     |
| ALT (U/L)            | Saxagliptin | 27 | 23.00    | 10.269         | 0.937|
|                      | Sitagliptin | 30 | 25.13    | 11.697         |     |
|                      | Vildagliptin| 30 | 25.47    | 13.364         |     |
|                      | Total       | 87 | 25.52    | 11.763         |     |
| Amylase (U/L)        | Saxagliptin | 27 | 63.33    | 22.675         | 0.646|
|                      | Sitagliptin | 30 | 67.13    | 20.416         |     |
|                      | Vildagliptin| 30 | 62.00    | 27.188         |     |
|                      | Total       | 87 | 64.18    | 23.456         |     |
| Lipase (U/L)         | Saxagliptin | 27 | 35.41    | 18.158         | 0.249|
|                      | Sitagliptin | 30 | 42.23    | 20.992         |     |
|                      | Vildagliptin| 30 | 34.10    | 18.713         |     |
|                      | Total       | 87 | 37.31    | 19.482         |     |

HbA1C: Hemoglobin A1c, ALT: Alanine transaminase, Std: Standard
duct glands can easily transform into PanIN-like lesions. At the same time, Butler et al. have reported that patients receiving incretin therapy experience exocrine pancreatic dysplasia and endocrine pancreatic cell proliferation. On the other hand, the limited number of patients and treatment involved in Butler et al. study as well as the lack of statistical data might have caused this link between therapy and cancer.

In previous studies, cases of pancreatitis associated with the use of DPP-4 inh have been presented as case reports. However, retrospective studies and meta-analyses have reported that these drugs are not statistically significant in terms of causing pancreatitis compared to other antidiabetic drugs. In the current study, although there was an increase in amylase and lipase in patients, no significant difference was seen in any patient possessing the characteristics of acute pancreatitis. In their study of acute pancreatitis among T2DM patients in Taiwan, Hsin-Chuo et al. determined the use of DPP-4 inh to be a risk factor for the presence of cholelithiasis and uncontrolled diabetes mellitus. On the other hand, in another retrospective cohort study conducted by Daisuke Yabe et al. in Japan among 93,280 antidiabetic patients who had been screened for acute pancreatitis and used 27,962 DPP-4 inh, no significant difference was observed in terms of acute pancreatitis development.

Studies have also emerged regarding the use of DPP-4 inh for elevating amylase and lipase from pancreatic exocrine enzymes. In a 3-month prospective study observing the amylase and lipase levels of 36 patients, 24 of whom were using DPP-4 inh and 12 of whom were taking other antidiabetic drugs, Tokuyama et al. observed an elevation in amylase and lipase levels among 11 out of 24 patients receiving DPP-4 inh that was regarded as statistically significant. In the present study, a baseline increase in amylase and lipase was observed in all groups. However, there was no statistically significant increase in the saxagliptin or vildagliptin groups (p>0.05), whereas a statistically significant increase was observed in the sitagliptin group.

The greater number of studies concerning sitagliptin in DPP-4-associated pancreatitis cases presented as case reports may be related to the longer treatment duration of sitagliptin in comparison to other DPP-4 inh. Still, some theoretical information (especially that derived from animal experiments) is available that indicates the cause of the increase in pancreatic enzymes with the use of DPP-4. Studies examining the relationship between sitagliptin and oxidative stress as well as inflammation have indicated that sitagliptin increases the levels of tumor necrosis factor-alpha in serum inflammatory stores. Moreover, it has been found to decrease oxidative stress in serum by decreasing serum IL-1β levels and reducing serum total malondialdehyde levels but not total antioxidant levels. Another study examining the effects of sitagliptin on oxidative

### Table 4. Comparison of laboratory parameters at the beginning and end of treatment

| Parameter     | Beginning Mean ± Std | 3 Months Mean ± Std | p     |
|---------------|----------------------|---------------------|-------|
| **Fasting glucose** |                      |                     |       |
| Saxagliptin   | 204.4±69.9           | 155.5±49.4         | 0.001 |
| Sitagliptin   | 190.7±66.1           | 162.7±52.9         | 0.018 |
| Vildagliptin  | 215.7±91.5           | 182.4±61.2         | 0.005 |
| **Postprandial glucose** |                   |                     |       |
| Saxagliptin   | 344.3±112.3          | 277.7±99.5         | 0.001 |
| Sitagliptin   | 275.9±114.6          | 251.7±108.7        | 0.098 |
| Vildagliptin  | 327.9±126.7          | 271.9±109.6        | 0.001 |
| **HbA1C**     |                      |                     |       |
| Saxagliptin   | 9.4±2.0              | 8.1±1.5            | 0.001 |
| Sitagliptin   | 8.9±1.6              | 7.8±1.4            | 0.001 |
| Vildagliptin  | 9.3±1.9              | 8.6±1.6            | 0.007 |
| **Amylase**   |                      |                     |       |
| Saxagliptin   | 60.7±21.5            | 63.3±22.7          | 0.400 |
| Sitagliptin   | 56.8±22.7            | 67.1±20.4          | 0.001 |
| Vildagliptin  | 56.0±21.7            | 62.0±27.2          | 0.174 |
| **Lipase**    |                      |                     |       |
| Saxagliptin   | 19.7±12.8            | 35.4±18.2          | 0.360 |
| Sitagliptin   | 25.3±17.0            | 42.2±20.9          | 0.001 |
| Vildagliptin  | 21.8±14.3            | 34.1±18.7          | 0.090 |
| **Creatinine**|                      |                     |       |
| Saxagliptin   | 0.9±0.3              | 0.9±0.2            | 0.564 |
| Sitagliptin   | 0.9±0.3              | 0.9±0.3            | 0.564 |
| Vildagliptin  | 0.9±0.3              | 0.9±0.2            | 0.564 |
| **ALT**       |                      |                     |       |
| Saxagliptin   | 23.1±10.9            | 26.0±10.3          | 0.037 |
| Sitagliptin   | 24.6±10.5            | 25.1±11.7          | 0.789 |
| Vildagliptin  | 22.6±9.4             | 25.5±13.4          | 0.096 |

HbA1C: Hemoglobin A1c, ALT: Alanine transaminase, Std: Standard
stress has reported that the total oxidant levels in diabetic rat pancreatic tissues did not change but oxidative stress increased due to decreased total antioxidant levels. This increased oxidative stress, which is likely to occur in the pancreas tissue, causes some inflammation in the exocrine pancreas. However, it is unclear whether this level can cause pancreatitis. Despite the inflammation and dysplastic changes in animal experiments examining the exocrine pancreas, the use of DPP-4 inh has been shown to increase function and mass in pancreatic beta cells.\(^5,\text{26}\)

Based on the above findings, one could assume that the use of DPP-4 inh may increased amylase and lipase levels in patients who do not exhibit symptoms of acute pancreatitis. Thus, DPP-4 inh should be used with caution in patients at risk for pancreatitis and pancreatic cancer. Moreover, patients using DPP-4 inh, especially sitagliptin, should be evaluated carefully for pancreatitis risk factors.

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