Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1133314
J Health Sci Med 2022; 5(5): 1424-1430

Effects of DPP-4 inhibitors on brain natriuretic peptide, neuropeptide Y, glucagon like peptide-1, substance P levels and global longitudinal strain measurements in type 2 diabetes mellitus patients

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Cite this article as: Asfuroğlu Kalkan E, Aydoğan Bİ, Dinçer İ. Effects of DPP-4 inhibitors on brain natriuretic peptide, neuropeptide Y, glucagon like peptide-1, substance P levels and global longitudinal strain measurements in type 2 diabetes mellitus patients. J Health Sci Med 2022; 5(5): 1424-1430.

ABSTRACT

Introduction: Previously, a significant relationship between saxagliptin treatment and increased rate of hospitalization for congestive heart failure was reported. We aimed to investigate effects of vildagliptin and saxagliptin on brain natriuretic peptide (BNP), neuropeptide Y (NPY), substance P (SP), glucagon like peptide-1 (GLP-1) levels and left ventricular global longitudinal strain (GLS), assessed by 3-dimensional speckle tracking echocardiography in uncontrolled type 2 Diabetes mellitus (T2DM).

Material and method: Thirty seven uncontrolled T2DM (HbA1c>7,5%) patients who were recently prescribed to either vildagliptin 50 mg BID (n=21) or saxagliptin 5 mg QD (n=16) were included in this study. Levels of BNP, NPY, SP, GLP-1 levels were measured at admission, first and third months of treatment. GLS was measured at admission and third month.

Results: In whole group, BNP and NPY values increased significantly at third month of treatment ($p< 0.001$, 0.004; respectively). In the vildagliptin group, BNP and NPY values increased significantly at third month of treatment ($p=0.02$ and $p=0.04$, respectively). In the saxagliptin group only BNP levels increased significantly ($p=0.015$). In both groups; SP, GLP-1 levels and GLS measurements did not change significantly during follow-up period.

Conclusion: The current study demonstrated that treatment with saxagliptin and vildagliptin, was associated with increased levels of BNP and NPY levels. No evidence of subclinical myocardial damage or cardiac dysfunction could be detected by GLS measurements. Since our study population had no previous clinical cardiac disorders, increases in BNP and NPY levels with these two DPP4 inhibitors can be considered as a safety signal.

Keywords: DPP-4 inhibitors, brain natriuretic peptide, neuropeptide Y, substance P, glucagon like peptide-1, 3 dimensional echocardiography

Oral presentation presented as abstract in 9th International Trakya Family Medicine Congress, 05-08 March 2020, Edirne, Turkey. Poster presentation presented as abstract in European Association for the Study of Diabetes (EASD) 3 October 2018, Berlin.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular diseases, and cardiovascular complications are the major cause of mortality in T2DM (1). Chronic heart failure (HF) is a frequent diabetes related cardiac complication that may also be related with glucose lowering medications (2-4). Cardiovascular safety is essential for approval of new glucose lowering drugs (5).

The risk of HF has been a controversial issue for DPP-4 inhibitors. "Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI 53)" trial revealed a significantly rising risk for HF hospitalizations in saxagliptin arm when compared to placebo (6). The "Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) " study also revealed an increased trend of HF hospitalizations, although this finding was not statistically significant (7). FDA added safety warnings about the risk of HF hospitalizations to labels of saxagliptin and alogliptin in 2016. Results from CVOTs of other DPP-4 inhibitors; omarigliptin (OMNEON),

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Received: 21.06.2022 **Accepted:** 09.08.2022

linagliptin (CARMELINA) and sitagliptin (TECOS-Trial Evaluating Cardiovascular) did not show an increased risk for HF (8-10). The only randomized-controlled trial for HF risk, "Effects of Vildagliptin on Ventricular Function in Patients With Type 2 Diabetes Mellitus and Heart Failure (VIVIDD)" study demonstrated an increase in left ventricular volumes, despite it did not have significant effect on left ventricular ejection fraction (11).

The causes of increased risk for HF hospitalizations in SAVOR-TIMI 53 and EXAMINE trials have not been explained yet. In SAVOR-TIMI 53 trial, HF hospitalizations were more frequent in patients with highest NT-proB-type natriuretic peptide (BNP) levels, so subclinical cardiac dysfunction was suggested as a risk factor for saxagliptin related worsening of HF (12). Also, DPP-4 enzyme has many substrates including neuropeptide Y (NPY), substance P, peptide YY, BNP, and stromal-derived factor 1 alpha (SDF-1 aka CXCL12), besides incretin hormones. All these molecules have several effects on cardiovascular system (13-20). Accumulation of these substrates by DPP-4 inhibition was suggested to cause alterations on cardiovascular system (13-20). Also, chance effect or statistical methodology errors were suggested as possible explanations for increased risk of HF in SAVOR-TIMI 53 and EXAMINE trials (21,22).

In the previous study, we purposed to study acute effects of vildagliptin and saxagliptin on brain natriuretic peptide (BNP), substance P (SP), neuropeptide Y and glucagon like peptide-1 (GLP-1) levels in patients with uncontrolled T2DM. Also left ventricular global longitudinal strain (GLS), assessed by 3-dimensional speckle tracking echocardiography.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara University Faculty of Medicine Clinical Researches Ethics Committee (Date: 09.02.2015, Decision no: 02-74-15) and written informed consent was obtained from all individual participants. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

Thirty seven uncontrolled insulin naïve type 2 DM (HbA1c >7.5%) patients who were started to use either vildagliptin 50 mg BID (n=21) or saxagliptin 5 mg QD (n=16) and completed the study period were enrolled in this study. All patients had metformin treatment for at least six months. A history of heart failure and coronary artery disease, previous treatment with insulin and DPP-4 inhibitors, stage 3-5 chronic kidney disease and active genitourinary infection were exclusion criteria. This study is a prospective study.

Biochemical parameters

Plasma NPY and BNP levels were measured with enzyme-linked immunosorbent assay (ELISA) method (Sunred Biological Technology. Shanghai, China). Substance P and GLP-1 were measured with ELISA method (Cloud-Clone Corp. Houston, USA). Biochemistry parameters were measured with ADVIA 2400 chemistry system assay (Erlangen, Germany) by Beckman Coulter DXC 800 device. Glycosylated hemoglobin (HbA1C) was measured with high-performance liquid chromatography (CinQ. Erlangen, Germany).

Levels of BNP, NPY, SP and GLP-1 were measured at admission, 1st - 3rd months of treatment.

Global Longitudinal Strain Measurements

GLS was measured at admission and 3rd month. Global longitudinal strain index measurements were performed by same experienced cardiologist. Standard echocardiography was performed with 4V multiphase array probe and Vivid E9 device (GE Vingmed, Horten, Norway). Basal echocardiographic measurements were performed according to the American Society of Echocardiography recommendations. Apical four chamber, three chamber and two chamber views were recorded at 60-100 frames/seconds rate for global longitudinal peak systolic strain measurements. Three cardiac cycles were archived from all views. Manual tracings of endocardium was performed by operator in all views and controlled during the systole. Global longitudinal strain was calculated with 18 segments model by dividing each view into six segments. Strain measurements were performed with the program on the device (EchoInsight, Epsilon, Ann Arbor, MI, USA).

Statistical Analyses

Statistical analysis was performed by using SPSS version 15 (IBM Corp, NY, US) for windows. Results were expressed as percentage of the patients or mean±SD where appropriate. The chi-square Fisher exact test used for categorical data. Student t test used for group data, and the Mann-Whitney U or Kruskal-Wallis tests used for nonparametric data. Correlations between continuous variables with and without normal distribution were assessed with Pearson and Spearman correlation tests, respectively. The changes of continuous variables over the follow-up period were assessed with paired test if data was normally distributed and with Wilcoxon test if data was not normally distributed. Friedman test or analyses of variance were performed for multiple comparisons. Changes in categorical variables over follow-up period were compared with McNemar test. Multiple comparisons were performed with Cochran Q test. $p<0.05$ was considered statistically significant.

RESULTS

Thirty-seven patients [18 male (48.6%) and 19 female (51.4%)] completed the study. Twenty-one patients were in vildagliptin and sixteen were in saxagliptin treatment arms. Baseline characteristics of patients in both groups were summarized in **Table 1**. There was no statistical significant difference between the treatment arms regarding to basal patient characteristics and biochemical parameters at the beginning of the DPP-4 treatment.

All patients had metformin treatment for at least six months prior to DPP-4 prescription. Eleven patients (52.3%) in vildagliptin arm and nine patients (56.2%) in saxagliptin arm had concomitant sulphonylurea administration.

Twenty-one patients (56%) had essential hypertension, seven (18.9%) had hyperlipidemia, and seven (18.9%) had hypertriglyceridemia. Seven patients were ex/current smoker.

Serum HbA1c, ALT and AST decreased significantly at the third month of DPP-4 treatment when compared to basal levels. The changes in laboratory parameters are summarized in **Table 2**.

BNP and NPY levels increased significantly at the 12th week of DPP-4 treatment when compared to basal measurements, in whole group. The levels of substance P, GLP-1 and global longitudinal strain measurements were similar to the basal at the end of the 12th week (**Table 3**).

Table 1. Basal characteristics and laboratory parameters of patients in two treatment arms.

Parameters	Vildagliptin arm	Saxagliptin arm	P value
Age, years	54.81±8.903	53.13±8.016	NS
BMI, kg/m²	29.13±3.11	28.93±3.97	NS
Body weight, kg	80.5±12.4	79.6±11.3	NS
Gender, F/M	11/10	8/8	NS
FPG, mg/dl	149.57±48.82	139.94±29.73	NS
Hemoglobin, g/dl	13.6±2.16	13.5±2.11	NS
HbA1c, %	8.17±1.33	7.88±1.25	NS
Creatinine, mg/dl	0.82±0.21	0.92±0.27	NS
ALT, UI/L	35.29±11.09	28.56±7.25	NS
AST, UI/L	25.90±6.74	20.94±4.04	NS
LDL, mg/dl	118.81±29.34	108.63±38.12	NS
HDL, mg/dl	43.14±8.32	41.94±11.16	NS
Triglyceride, mg/dl	188.29±115.42	179.56±92.32	NS
TSH, mIU/L	1.92±1.35	1.87±1.12	NS

ALT: alanine aminotransferase, AST: aspartate aminotransferase , LDL: Low density lipoprotein, HDL: high density lipoprotein,BMI: Body mass index; F/M: Female/Male; FPG: Fasting plasma glucose; HbA1C: Glycosylated hemoglobin; NS: non–significant; TSH: thyroid stimulating hormone.

Table 2. Changes in laboratory parameters during follow–up period in whole group.

Parameters	Basal	12th week	P value
FPG, (mg/dL)	145.41±41.42	134.89±32.22	NS
BMI, (kg/m²)	28.98±3.49	28.3±3.46	NS
Body weight, (kg)	80.2±12.6	79.5±12.7	NS
Hemoglobin, g/dl	14.19±1.75	14.16±1.49	NS
HbA1c, (%)	8.05±1.28	7.3±1.1	0.004
Creatinine, mg/dl	0.84±0.26	0.85±0.21	NS
ALT, UI/L	32.28±12.69	27.0±10.04	0.002
AST, U/L	23.76±6.9	19.89±4.8	<0.001
LDL, mg/dL	114.41±33.32	101.81±26.17	NS
HDL, mg/dL	42.62±9.52	44.14±9.29	NS
TG, mg/dL	181.51±104.75	185.11±88.51	NS
TSH, mIU/mL	1.90±0.74	1.71±0.82	NS

ALT: alanine aminotransferase, AST: aspartate aminotransferase , LDL: Low density lipoprotein, HDL: high density lipoprotein,BMI: Body mass index; F/M: Female/Male; FPG: Fasting plasma glucose; HbA1C: Glycosylated hemoglobin; NS: non–significant; TG: triglyceride TSH: thyroid stimulating hormone.

Table 3. Changes in BNP, NPY, GLP–1, SP levels and GLS measurements at the 12th week of treatment.

Parameter	Whole group	P value*	Vildagliptin	Saxagliptin	p
BNP (ng/L)					
Basal	11.0 (3.71–44.0)	P<0.001	10.1 (5.2 – 36.0)	8.5 (3.7 – 44.0)	0.020/0.015
4th week	19.0 (2.38– 37.0)		17.7 (5.8 – 36.0)	14.0 (2.4 – 37.0)	
12th week	21.7 (2.36–60.89)		20.5 (6.4 - 60.9)	18.4 (2.4 – 50.0)	
NPY (ng/L)					
Basal	8.1 (2.0– 44.0)	p=0.004	9.6 (4.3 - 27.7)	7.5 (2.0 – 44.0)	0.047/NS
4th week	12.9 (4.4–32.9)		14.0 (4.4 - 32.9)	12.4 (4.6 – 23.0)	
12th week	15.0 (2.6–42.1)		17.0 (3.92 - 42.1)	14.0 (2.6 – 37.0)	
GLP–1 (pg/mL)					
Basal	21.0 (8.9–33.0)	NS	23.5 (12.1 – 33.0)	19.9 (8.9 - 31.0)	NS/NS
4th week	21.0 (10.0–35.8)		22.0 (10.0 - 35.8)	20.2 (10.0 - 34.2)	
12th week	19.1 (9.0–33.2)		19.1 (10.5 - 33.2)	20.5 (9.0 – 31.0)	
SP (pg/mL)					
Basal	22.5 (5.3–46.5)	NS	17.4 (5.3 - 46.5)	27.5 (10.6 - 39.3)	NS/NS
4th week	22.0 (7.4–47.9)		24 (7.4 - 47.9)	18.0 (8.0 - 40.5)	
12th week	28.4 (8.0–46.0)		29.4 (9.4 – 39.0)	27.5 (8.0 – 46.0)	
GLS (%)					
Basal	–16.3 (–10.3 /–21.6)	NS	-16.34±2.83	-16.41±2.80	NS/NS
12th week	–16.2 (–11.1 /–21.7)		-15.82±2.40	-16.72±2.83	

BNP: Brain natriuretic peptide; GLP–1: Glucagon like peptide–1; GLS: Global longitudinal strain; NPY: Neuropeptide Y; SP: Substance P, NS: Non–significant.
*p values belong to comparison of 12th week vs. basal measurements.

Serum BNP level increased significantly at the end of the treatment when compared to basal in vildagliptin and saxagliptin treatment groups (p=0.02 and p=0.015, respectively). Serum NPY level increased significantly in only vildagliptin group at the 12th week when compared to basal measurement (p=0.047). Serum SP, GLP-1 levels and GLS measurements were similar to the basal values at the 12th week of treatment in both groups (**Table 3**).

Serum BNP levels of 16 patients (76.2%) in vildagliptin arm and 13 patients (81.3%) in saxagliptin arm increased during the follow-up period. Serum NPY levels of 17 patients (80.9%) in vildagliptin arm and 12 patients (75%) in saxagliptin arm increased during the follow-up period.

DISCUSSION

Our study showed that the treatment with saxagliptin and vildagliptin, were associated with increased levels of BNP. Substance P and GLP-1 levels were not changed during the follow-up period. Vildagliptin treatment was also associated with increased NPY levels. Nevertheless, GLS measurements were stable during the treatment period and patients did not need hospitalization for heart failure.

The CVOTs of DPP-4 inhibitors have not showed increased risk for MACE, whereas their effects on the risk of HF hospitalizations have been conflicting (6,8-11,23,24). A significant increase in the risk of hospitalization for HF was observed with saxagliptin treatment in SAVOR-TIMI 53 trial (6). A secondary analysis of the EXAMINE trial also demonstrated an increased trend towards heart failure hospitalizations with alogliptin among patients without prior HF (25). Cardiovascular trials of omarigliptin, sitagliptin and linagliptin showed similar safety profile with placebo with regard to MACE and heart failure hospitalizations (8-10). Some meta-analyses of CVOTs showed significant increase of heart failure with DPP-4 inhibitors, but their results were attributed to large cohort of SAVOR-TIMI 53 trial (26-27). Consistent with this opinion, a meta-analysis by Kongwatcharapong et al. (28) included 54 randomized controlled studies and suggested that use of saxagliptin was associated with heart failure, whereas other DPP-4 inhibitors were not. Otherwise, a large number of studies reported at least non-inferiority of DDP-4 versus placebo or other antidiabetics with regard to HF risk (3,29-32). The data from these meta-analyses were obtained by indirect comparisons, as head to head comparisons were not available. In the present study, patients enrolled the study without prior HF and observed that vildagliptin and saxagliptin treatments did not cause HF in a three months follow-up period.

The cause of increased risk for HF hospitalizations with saxagliptin treatment has not been understood yet. One hypothesize was a chance effect or a statistical error in SAVOR-TIMI trial. The inappropriate statistical methods were suggested as the cause of increased HF hospitalization risk (22). In the study of Kaneko et al. (21), authors re-evaluated the TECOS, EXAMINE and SAVOR-TIMI study groups for cardiovascular risk including hospitalization for HF risk with a different method and did not find any significant risk. Deterioration of endothelial function by DPP-4 inhibitors was suggested as a potential cause for HF previously (33). In the study of Ayaori et al. (33), it was found that flow mediated dilatation was significantly reduced with sitagliptin and alogliptin treatments. Authors emphasized that reduced GLP-1 metabolite by DPP-4 inhibition may be the cause of endothelial dysfunction (16,33). However, this result was not supported by van Poppel's study as they showed that endothelial function was improved with vildagliptin treatment (34). A class effect caused by accumulation of enzyme substrates has been widely suggested as a possible mechanism by which DPP-4 inhibitors may increase the risk of HF. The DPP-4 enzyme is expressed by many tissues and organs, and it is responsible for cleavage of many peptide hormones and cytokines (35,36). Substance P and NPY are the substrates of DPP-4 and they stimulate the sympathetic activity (14,20). Both SP and NPY were suggested to be related with myocardial fibrosis and adverse remodelling (17,37). In the study of Hubers et al. (19), sitagliptin treatment potentiated the norepinephrine release and NPY induced vasoconstriction. Consistently, a clinical study by Wilson et al. (38), showed that DPP-4 inhibition by sitagliptin increased NPY and norepinephrine levels. The increase in norepinephrine concentration was through a substance P receptor-dependent mechanism and under renin-angiotensin system blockage (38). The subgroup analysis of beta-blocker users in SAVOR-TIMI 53 trial demonstrated that hospitalization rates for HF were not increased in this group (24). This finding was suggested as an evidence of relation between HF and increased sympathetic activation by DPP-4 substrates (13,24). Treatment of patients with HF was not optimized with beta blockers and this may be another evidence for the impact of increased sympathetic activity by saxagliptin (13). The increase in HF hospitalization rate was associated with prior chronic kidney disease, HF and high basal BNP levels in SAVOR-TIMI 53 trial. Subclinical cardiac dysfunction was suggested as a risk factor for saxagliptin related worsening of HF (12). In our study, we did not observe change in substance P level over the treatment period but NPY level was increased in both groups. However, this finding was not associated with an evidence of increased subclinical cardiac dysfunction, as GLS measurements did not change over the treatment period.

The GLP-1 is the incretin substrate of DPP-4 and not only intact GLP-1 but also its metabolite were suggested to be biologically active and decrease the myocardial ischemia (16,18). Conversely, GLP-1 potentiation by DPP-4 inhibition is related with increased cAMP in myocardium and this alterations were suggested as a possible cause of heart failure exacerbation (39). Increased GLP-1 levels were also suggested to be associated with inflammation (40). Thus, impact of increased GLP-1 and decreased GLP-1 metabolite on cardiovascular system by DPP-4 enzyme inhibition has not been fully understood yet (41). In the present study, there was no significant changes in GLP-1 levels with neither saxagliptin, nor vildagliptin over a 12 weeks follow-up period.

Brain natriuretic peptide is another substrate for DPP-4 enzyme and a marker for heart failure (15). A study by Fadini et al. (42), reported that linagliptin treatment was not associated with acute effects on BNP and NT-proBNP levels. The change in BNP levels during DPP-4 treatment was evaluated in SAVOR-TIMI and EXAMINE study groups, but the treatment period was long, so the results did not reflect acute changes (7,24). Results of SAVOR-TIMI and EXAMINE trials were controversial, as both increased and decreased NT-proBNP levels were reported (6,7). A recent meta-analysis evaluated 9 randomized controlled trials with 3056 patients, by Mu et al. (43). They reported that DPP-4 inhibitors show no significant effect on BNP or NT-pro-BNP. Also they demonstrared that these agents shows no stronger effect than traditional antidiabetic agents in T2DM.

In our study, we observed that vildagliptin and saxagliptin treatments were both related with elevated levels of BNP, which may be a signal for HF.

The CVOTs of DPP-4 inhibitors were not designed to evaluate the risk of HF specifically and "hospitalization for HF" was a secondary outcome (6,8–10). Effects of DPP-4 inhibitors on echocardiographic parameters were evaluated in a limited number of studies (11,44,45). The only randomized-controlled trial for HF risk was performed with vildagliptin (VIVIDD study) and demonstrated an increase in left ventricular volumes when compared to placebo, despite it did not have significant effect on left ventricular ejection fraction (11). The baseline BNP levels and end-diastolic volumes were higher in vildagliptin arm. However, the significance or cause of this change could not be explained, and adverse cardiac remodeling could not be excluded. A randomized study evaluated changes in echocardiographic parameters over a 6 months treatment period with sitagliptin and showed that sitagliptin was not associated with improvement in left ventricle diastolic functions (44). On the other hand, in a pilot study by Leung et al. (45), DPP-4 inhibition was related with improved left ventricular function and GLS measurements at 12 months treatment period. Some of the previous studies, revealed favorable effects of DPP-4 inhibitors on diastolic functions (45,46). On the contrary, a recent meta-analysis by Zhang et al. (47), revealed that DPP-4 inhibitors had a negative impact on left ventricular end diastolic volume without increased ejection fraction. In our study, we evaluated GLS to assess any acute subclinical changes over a three months treatment period. Neither saxagliptin, nor vildagliptin were related with acute changes in GLS measurements.

The major limitations of the current study were the small sample size and lack of inclusion of patients with prior HF.

CONCLUSION

Our study showed that treatment with saxagliptin and vildagliptin was related with increased levels of BNP and NPY levels. However, subclinical myocardial damage or cardiac dysfunction could not be detected by GLS measurements assessed by 3-dimensional speckle tracking echocardiography over a 12 weeks period. There was no history of clinical cardiac disorder in our study population. Therefore, increases in BNP and NPY levels with vildagliptin and saxagliptin can be considered a safety signal. Patients with known heart problems are needed to clarify this.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara University Faculty of Medicine Clinical Researches Ethics Committee (Date: 09.02.2015, Decision no: 02-74-15).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: This research was funded by the Scientific Research Foundation of Ankara University (Grant number 15B0230006).

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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