Original Article

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Vildagliptin Treatment on the Portal Venous Pressure and Hepatosteatosis in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Objective: This study investigated how vildagliptin (a di-peptidyl peptidase 4 inhibitor) affects portal vein pressure and hepatosteatosis in patients with type 2 diabetes mellitus.

Methods: This cross-sectional study evaluated the use of specific drugs for at least 3 months on two groups of type 2 diabetes mellitus cases. Group 1 used metformin and gliclazide, Group 2 used the same amounts of metformin and gliclazide, with the addition of vildagliptin. Using Doppler ultrasound, all cases were measured for portal vein flow velocity, portal vein flow and portal vein diameter. Degree of hepatosteatosis was also recorded.

Results: A total of 97 patients completed the study. The study finished with 49 type 2 DM patients in Group1 (20 men, 29 women) and 48 patients in Group2 (20 men, 28 women. No significant difference was found in term of age, gender, BMI, HbA1c, mean arterial pressure, LDL-C, HDL-C or triglyceride levels in two groups.Portal vein flow velocity, portal vein flow volume, and portal vein diameter of all cases were measured by Doppler ultrasound in both groups. No significant difference was found between the groups (respectively p=0.92, p=0.60, p=0.92). There was no significant difference between groups regarding to ultrasonographic grading of hepatosteatosis.

Conclusion: Treating type 2 diabetes mellitus patients with vildagliptin for had no effect on portal vein hemodynamics and hepatosteatosis as assessed with Doppler ultrasound. Further long-term studies with better evaluation methods are needed to demonstrate any expected beneficial effect of vildagliptin on portal hemodynamics and hepatosteatosis.

Keywords: Di-Peptidyl peptidase 4 inhibitors, vildagliptin, portal vein pressure, hepatosteatosis, type 2 diabetes mellitus

Introduction

Recent years have seen the development of drugs that increase plasma incretins for treatment of type 2 diabetes mellitus (DM). Incretins are secreted as an intestinal hormone by entero-endocrine cells immediately after meals for the purpose of regulating glucose. The two known incretins are glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1). Both of the incretins are rapidly inactivated by the enzyme named dipeptil peptidase 4 (DPP-4). Developed DPP-4 inhibitor drugs increase the plasma concentrations of GIP and GLP-1 by preventing their degradation by inhibiting the pertinent enzyme (1, 2).

Although DPP-4 inhibitors mainly affect the pancreatic gland, they also affect the gastrointestinal tract, central nervous system, bone, adipose tissue, and the cardiovascular system (1, 2). They both incretins reduce intestinal motility, extend the

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time of gastric emptying, and suppress gastric acid secretion, particularly in the gastrointestinal tract (3, 4). These effects may cause slight to severe nausea, vomiting, or bloating.

A previous study on dog fetus cell culture found that production of nitric oxide (NO) increased due to the incretin GIP, which in turn resulted in increased portal venous flow (5). NO is a potent short-lived vasodilatatory radical that plays an important role in the regulation of vascular tone (6). Increased NO secretion is one of the main responsible mediators that occurred from splanchnic vein hyperemia and vasodilatation of the portal vein.

In recent years, it was shown that ischemic injury plays an important role in the etiology of non-alcoholic fatty liver disease (NAFLD), the specific liver pathology of metabolic syndrome (7, 8). As research continues for definitive treatment, current treatment of fatty liver disease is directed against etiological subgroups such as obesity, hypertension, hyperlipidemia, and type 2 diabetes mellitus. Treatments that demonstrate efficacy in the treatment of type 2 DM and in prevention of ischemic injury in the liver may be a novel treatment alternative for patients with NAFLD.

We could not find any study till date in the literature that investigate the effect of NO synthesis on liver and portal vein that is expected to increase in patients using vildagliptin. This study investigated the effect of the used type 2 DM drug, vildagliptin, a DPP-4 inhibitor, on portal hemodynamics and hepatosteatosis.

Methods

Patients

This cross-sectional research was designed to evaluate two groups, each with 50 type 2 DM cases, who were followed for at least 3 months and used the same drugs at the Outpatient Clinic. Patients were randomly assigned to treatment groups. The first group (Group 1) consisted of patients that used metformin (1000 mg bid) and gliclazide (60 mg qd). The second group (Group 2) consisted of patients that used vildagliptin (50 mg bid) in addition to the same amount of metformin and gliclazide since their glycated haemoglobin (HbA1c) was detected at 7% or higher. The patients were prospectively assigned to each of these two groups for the purpose of this study. Patients with type 2 DM older than 18 years that used metformin and gliclazide or metformin, gliclazide and vildagliptin for at least 3 months were included in the study. Patients who have diseases that may affect the portal vein pressure such as chronic liver disease, chronic renal failure, active infection and patients using certain drugs which may affect portal pressure such as propronalol, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and isosorbit monohydrate were excluded from the study. Patients with body mass index (BMI) over 40 kg/m^2 and that used alcohol and cigarettes were also excluded from the study. For each subject, body mass index was calculated and recorded along with arterial blood pressure, height, and weight. Also low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, and HbA1c levels were measured. Patients were questioned for history of other known diseases, operations, and use of other pharmaceutical drugs.

This study protocol was in accordance with the declaration of Helsinki and was approved by the Ethics Committee of Bezmialem Vakıf University. Written informed consent was obtained from each participant before commencement of the study (ClinicalTrials. gov Identifier: NCT01963130).

Echo-Doppler Ultrasound

Patients were examined in the left decubitus position with a Logiq 9 Review (GE, Milwaukee, WI, USA) ultrasound device and a 3.5-mHz convex transducer probe was used. Gray scale and color Doppler features were used. First, all segments of the liver were examined and the presence and degree of hepatosteatosis was recorded. Next portal vein measurements were made at the level of the portal confluence. Doppler angle was maintained at 30°-60°. Doppler gain and filter settings were adjusted. During the mid-inspiratory phase, the spectrum of portal vein was recorded for at least 5 seconds and measurements were performed through this wave pattern. Portal vein diameter, flow pattern, flow velocity, and flow rate were evaluated. Measurements were repeated three times and the average of these three measurements was recorded (9).

Blood samples were drawn after 12 hours of fasting in the morning hours, i.e., between 8:00 and 9:00 a.m., in the laboratory of Bezmialem Vakif University Hospital. Lipid profile was measured by chemiluminescent immunoassay method, using"Beckman Coulter" device. Glycated haemoglobin (HbA1c) levels were measured by turbidimetric inhibition immunoassay (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical analysis

Statistical analyzes of data were performed using the Statistical Package for Social Sciences for Windows 13.0 (SPSS Inc., Chicago, IL, USA). Mean, median, and standard deviation were used for descriptive statistical evaluation where appropriate; t-tests compared normally distributed parameters. Mann-Whitney U test was used to compare non-normal distributed parameters, and Chi-square test was used to compare proportional data. Two-sided p value <0.05 was considered significant.

Results

A total of 97 patients completed the study. Three patients were dropped from the study because they did not accept examination by Doppler ultrasound. The number of enrolled cases in the study reduced to 49 cases with type 2 DM in Group 1 (20 men, 29 women) and 48 cases in Group 2 (20 men, 28 women). Ages ranged from 35 to 79 years old. No

Table 1. The demographic and laboratory characteristics of cases by group

	Group 1 (n=49)	Group 2 (n=48)	p
Age (years)	57±9.9	54.7±9.5	0.26
BMI (kg/m²)	30.1±5.3	31.1±6.8	0.67
HbA1c (mmol/mol)	54±12	55±9	0.53
HbA1c (%)	7.07±1.07	7.23±1.3	
MAP (mmHg)	120±16.4	125±12.3	0.62
LDL-C (mg/dL)	135 ± 36	133 ± 23	0.9
Triglyceride (mg/dL)	206±16.8	192±24.4	0.58
HDL-C (mg/dL)	28±12.6	32±14.2	0.55

Group 1: Cases who use metformin (2x1000 mg) and gliclazide (1x60 mg), Group 2: Cases who use metformin (2x1000 mg), gliclazide (1x60 mg) and vildagliptin (2x50 mg), MAP: mean arterial pressure; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

Table 2. Portal vein flow velocity, portal vein flow, and portal vein diameter by group

	Group 1 (n=49)	Group 2 (n=48)	p
Portal vein flow velocity (cm/s)	7.6±1.6	7.8±2.9	0.6
Portal vein flow volume (mL/min)	482.4±14	478.5±23	0.92
Portal vein diameter (mm)	11.47±1.6	11.43±1.8	0.92

Group 1: Cases who use metformin (2x1000 mg) and gliclazide (1x60 mg), Group 2: Cases who use metformin (2x1000 mg), gliclazide (1x60 mg) and vildagliptin (2x50 mg).

Table 3. The comparison of hepatosteatosis sign and degree of hepatosteatosis by group

Stage	Group 1 (n=49)	Group 2 (n=48)	p
Stage 0	8 (16.6)	14 (29.2)	0.13
Stage 1	20 (40.8)	18 (37.5)	0.45
Stages 2-3	21 (42.9)	16 (33.3)	0.33

Group 1: Cases who use metformin (2x1000 mg) and gliclazide (1x60 mg), Group 2: Cases who use metformin (2x1000 mg), gliclazide (1x60 mg), and vildagliptin (2x50 mg).

significant difference was found in term of age, gender, BMI, HbA1c, mean arterial pressure, LDL-C, HDL-C or triglyceride levels in two groups. Table 1 shows the age of the patients and parameters of metabolic syndrome.

Portal vein flow velocity, portal vein flow, and portal vein diameter of all cases were measured by Doppler ultrasound in both groups. No significant difference was found between the groups (Table 2). There was no significant difference between groups regarding to ultrasonographic grading of hepatosteatosis (Table 3).

The duration of Group 2 vildagliptin use was 7.8±4.65 (range 3-17 months) months. Seven patients and nine patients were using atorvastatin in group 1and group 2 respectively.

Discussion

It is known that hepatosteatosis accompanied in the majority of patients with type 2 diabetes mellitus. In some cases with hepatosteatosis, developed steatohepatitis characterized by elevated liver enzymes and liver inflammation. Steatohepatitis is considered to be important in the etiology of the disease classified as cryptogenic liver cirrhosis (10). Another point is the release of NO which is an important vasodilator. NO is secreted mostly from endothelial cells and smooth muscles. It causes vasodilatation in many vessels as well as in the portal vein. NO also shows effects for the prevention of cirrhosis by reducing sinusoidal resistance, antifibrosis and antithrombosis. However, when over-secreted in patients with cirrhosis, it contributes to the hyperdynamic circulation and portal hypertension by means of vasodilatation and increased portal blood flow. At the same time, NO improves the growth of collateral artheries and causes collateral blood flow (6-8). This can contribute to variceal bleeding, one of the most feared complication in cirrhotic patients. Vildagliptin, used in the treatment of type 2DM, may lead to an increase in NO release by increasing incretins (11). In one study after icretin was given to the canine cell culture, it was found that NO levels in the portal vein increased (5). Another study demonstrated decreased levels of serum acetyl di-methyl arginine, which is recognized as an indirect indictor of NO elevations, in subjects receiving vildagliptin (12). In one another study that measured aortic and glomerular NO levels in obese rats using saxagliptin, showed that enhanced glycemic control with DPP4 inhibition improved NO release (13). In our study we aimed to determine the effects of increased NO levels on portal vein pressure and hepatic steatosis in patients with type 2 DM using vildagliptin for longer than three months.

In our study, the two groups exhibited no difference in terms of parameters of metabolic syndrome. We could not find any effect of vildagliptin on portal venous flow, portal vein diameter, or flow rate. It could be that in treatment of diabetes, the process required for vildagliptin to exhibit a positive effect on hepatosteatosis and hemodynamics of the portal vein may require a longer period of time than the 3 months of this study period. When we evaluated the results, NO secretion is expected to increase in diabetics using vildagliptin. However, our study did not confirm a reduction in portal vein pressure by doppler ultrasound. This situation can be interpreted in three ways. Firstly, DPP-4 inhibitors increase NO release, but decrease the release of glucagon. While the release of NO cause vasodilatation in portal vein, on the contrary decreased glucagon levels cause vasoconstriction in the portal vein (14, 15). As a result, the result is meaningless because vildagliptin may have multiple effects via different mechanisms. Secondly, the majority of patients with type 2 DM are known to have

metabolic syndrome. It is thought that the release of NO decreases depending on the endothelial dysfunction in patients with metabolic syndrome (7, 8). As a result, the result is meaningless because most of these patients have metabolic syndrome and this does not increase the release of NO. Finally, even if the use of vildagliptin increase the release of NO in portal vein, this increase may not be sufficient to make changes in portal pressure.

Invasive angiographic examination is the gold standard for the measurement of hepatic venous pressure gradient and portal vein pressure; however, abdominal Doppler ultrasound is non-invasive and cheap, particularly for evaluation of patients with hepatic dysfunction. Doppler ultrasound is therefore a major diagnostic tool for noninvasive evaluation of hepatic vascular hemodynamics (16-18). In a study including 375 patients with portal hypertension, the sensitivity and specificity of parameters of portal vein by Doppler ultrasonography for demonstration of portal hypertension were 80% and 80%, with a weak correlation between Doppler ultrasound findings and portal pressure. There was also a correlation between Doppler ultrasound findings and the severity of portal hypertension until occurrence of collaterals (17). In our study, no case had clinical or laboratory findings that support the development of collaterals; therefore, we may suggest Doppler USG as an appropriate, non-invasive method for assessment of portal vein pressure.

Patients who used vildagliptin treatment did not differ significantly with regards to hepatosteatosis grade. In the control group, there were no significant differences in hepatosteatosis or serum ALT levels. A published review on the effects of DPP-4s on the liver included studies which report that DPP-4 inhibitors corrected hepaticsteatosis as well as those which described a close association with hepaticsteatosis (19). A study investigating the effects of sitagliptin, a DPP-4 inhibitor, in patients with moderate hepatic impairment found that the drug was safe and did not cause clinical deterioration (20). Our results did not indicate a significant increase in hepaticsteatosis.

Study limitations

Since in our study exclusion criteria is kept wide to reduce the risks that affect portal pressure, the number of patients is limited. Declaration of patients and their relatives were taken into account since levels of GLP-1 in plasma cannot be measured. Therefore, there was not an objective criterion that shows if the patients use the drug or not. We could measure the level of portal pressure and hepatic steatosis before vildagliptin and 3 months after initiation of the drug. Three-month period may be considered insufficient to detect the effect of vildagliptin on portal pressure by Doppler imaging. But by our cross sectional study, patients using vildagliptin for an average of 7 months enrolled in the study. Another point is that there was no study showing how sensitive Doppler ultrasound is to demonstrate the short-term change in portal flow.

Conclusion

A treatment of type 2 DM patients with the incretin vildagliptin for at least 3 months had no effect on portal vein hemodynamics as assessed with Doppler ultrasound. Further long-term studies with better evaluation methods are needed to demonstrate the expected potential beneficial effect of vildagliptin on portal hemodynamics and hepatosteatosis.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Bezmialem Vakif University (07.05.2014 Decision No: 8/1 Issue: 7130664/020-01-04/111).

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

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