



Effects of 18-month Vildagliptin Treatment on Portal Vein Pressure and Hepatosteatosi

On Sekiz Aylık Vildagliptin Tedavisinin Portal Ven Basıncı ve Hepatosteatoz Üzerine Etkisi

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ABSTRACT

Objective: Patients with type 2 diabetes have an increased tendency to develop hepatosteatosi. The effects of drugs used to treat diabetes on the liver, regardless of the disease, are unknown. The aim of this study was to investigate the effects of vildagliptin, a dipeptidyl peptidase-4 inhibitor, on the portal vein pressure and hepatosteatosi in patients with type 2 diabetes in the 18 months of follow-up.

Methods: Patients to whose treatment vildagliptin was added while they were on therapy with metformin and gliclazide for type 2 DM the vildagliptin group were included. As the control group, 49 patients with type 2 DM treated with metformin and gliclazide were included. These patients were followed up for 18 months. These patients were followed for 18 months and their pre-treatment and post-treatment examinations were repeated. Portal vein diameter, portal vein flow and portal vein velocity were calculated to evaluate portal vein pressure with the same Doppler ultrasonography (US) by the same radiologist. In the same session, the liver steatosis stage of all patients was evaluated with US and recorded. The data before treatment and the data 18 months after treatment were compared.

Results: Nineteen patients completed the study in the study group, while 10 patients completed the study in the control group. A significant increase in portal vein flow velocity and vein diameter was found in the study group when portal vein parameters were compared before and after treatment ($p<0.001$, $p=0.035$, respectively). There

ÖZ

Amaç: Tip 2 diyabet hastalarında hepatosteatoz gelişme eğilimi fazladır. Diyabet tedavisinde kullanılan ilaçların hastalıktan bağımsız olarak karaciğer üzerine etkileri çok bilinmemektedir. Bu çalışmada amacımız bir dipeptidil peptidaz-4 inhibitörü olan vildagliptinin uzun süreli takibinde karaciğer yağlanması ve portal ven basınç parametreleri üzerine etkisini araştırmaktır.

Yöntemler: Bu çalışma prospektif, kontrollü gözlemsel bir çalışma olarak tasarlandı. Çalışmaya benzer demografik ve klinik özellikleri olan tip 2 diyabet hastaları alındı. Çalışma grubu metformin ve gliclazide tedavisine, vildagliptin eklenen hastalardan oluşturuldu. Kontrol grubuna ise metformin ve gliclazide kullananlar alındı. Bu hastalar 18 ay takip edildi ve tedavi öncesi ile tedavi sonrası tetkikleri tekrarlandı. Tüm hastaların aynı radyoloji uzmanı ve Doppler ultrasonografi (US) cihazı ile portal ven basıncını değerlendirmeye yönelik olarak portal ven çapı, portal ven debisi ve portal ven akım hızı hesaplandı. Aynı seansta tüm hastaların karaciğer steatoz evresi US ile değerlendirilerek kaydedildi. Tedavi öncesi ile 18 ay sonraki veriler karşılaştırıldı.

Bulgular: Çalışma grubunu 19 hasta tamamlarken kontrol grubunu 10 katılımcı tamamladı. Çalışma grubunda portal ven parametreleri tedavi öncesi ile tedavi sonrası kıyaslandığında portal ven akım hızında ve ven çapında anlamlı artış bulundu ($p<0,001$, $p=0,035$, sırasıyla). Portal ven debisinde anlamlı fark saptanmadı. Kontrol grubunda ise portal ven çapında anlamlı artış olmasına rağmen

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was no significant difference in portal vein flow volume. In the control group, no significant changes in flow velocity and flow volume were detected, although there was a significant increase in portal vein diameter ($p=0.04$, $p=0.07$, $p=0.14$, respectively). There were no significant changes in vildagliptin group before and after treatment in terms of hepatosteatosis ($p=0.41$). There were no significant changes between control and study groups in terms of hepatosteatosis after 18 months of treatment.

Conclusion: As a result, we did not find any significant changes in the parameters of portal vein pressure with vildagliptin use. We think that vildagliptin has no effect on hepatosteatosis.

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

akım hızında ve debisinde anlamlı değişiklik saptanmadı ($p=0,04$, $p=0,07$, $p=0,14$, sırasıyla). Hepatosteatoz değerlendirildiğinde vildagliptin grubunda tedavi öncesi ve sonrası anlamlı bir değişiklik saptanmadı ($p=0,41$). Kontrol grubu ile karşılaştırıldığında 18 aylık tedavi sonrası hepatosteatozda anlamlı değişiklik bulunmadı.

Sonuç: Sonuç olarak vildagliptin kullanımı ile portal ven basıncını gösteren parametrelerde anlamlı değişim saptamadık. Ayrıca vildagliptinin hepatosteatoz üzerine etkisinin olmadığını düşünmekteyiz.

Anahtar Sözcükler: Di-peptidyl peptidase 4 inhibitors, vildagliptin, portal vein pressure, hepatosteatosis, tip 2 diabetes mellitus

Introduction

Incretin-based therapies are agents that have been developed for the treatment of type 2 diabetes mellitus (DM). Improved glucoregulation has been observed following decreased break down or exogenous administration of an incretin hormone, glucagon-like peptide-1 (GLP-1). The advent of dipeptidyl peptidase-4 (DPP-4) inhibitors allows prevention of GLP-1 break down, thus increases its plasma concentration. Although these DPP-4 inhibitors act primarily on the pancreatic gland, they also exert effects on non-pancreatic organs (1,2). The gastrointestinal system in particular, as well as the central nervous system, bone, fatty tissue and the cardiovascular system are the most affected organs (3,4). This includes portal vein (PV) pressure and hepatic steatosis. In dog cell culture studies, there is an increased nitric oxide (NO) release from endothelial cells associated with the increased levels of an incretin hormone, gastrointestinal peptide (GIP), and increased PV flow (5). NO is a short-living vasodilator with a significant role in the regulation of the vascular tonus (6). The effects of vildagliptin on PV pressure and hepatosteatosis were investigated previously (7). However, a long-term prospective study was not performed. In our study, we aimed to investigate the effects vildagliptin (DPP-4 inhibitor) on portal system pressure and hepatic steatosis by means of laboratory tests and portal system Doppler ultrasonography (US) in patients with type 2 DM following 18-month therapy.

Method

The study was designed as a prospective observational study. The study included patients to whose treatment vildagliptin (2*50 mg) was added while they were on therapy with metformin (2*1000mg), gliclazide (1*60 mg) for type 2 DM (the vildagliptin group). As the control group, patients treated with metformin (2*1000 mg) and gliclazide (1*60 mg) were included (the control group). Complete blood counts (CBCs) and biochemistry tests were performed in all subjects and their demographics were recorded. Each subject's PV diameter, PV flow volume and PV flow velocity were measured with the same doppler US device and by the same radiologist to evaluate PV pressure. Hepatic steatosis was also graded with US during the

same session. Both the vildagliptin group and the control group were followed up for a period of 18 months and subjects who were still on the same treatment at the end of 18 months and who did not meet the exclusion criteria underwent repeat PV doppler US. These subjects' CBCs and biochemistry tests were also repeated and demographics were recorded again. Of these subjects, vildagliptin users were evaluated in the pre-treatment and post-treatment periods. The subjects in the control group who did not receive vildagliptin were evaluated in the pre-treatment and post-treatment periods. The obtained results were compared at the end of the study.

The study included patients who were at least 18 years of age, treated with gliclazide and metformin only or with vildagliptin added to gliclazide and metformin therapy. Patients with chronic liver disease which may increase portal pressure, congestive heart failure, chronic renal failure, chronic obstructive pulmonary disease, vasculitis and active infectious disease were excluded. In addition, patients receiving agents that are known to act on portal pressure including beta-blockers and isosorbide mononitrate were also excluded. Further exclusion criteria included patients treated with agents that are known to induce NO release including angiotensin converting enzyme blockers, angiotensin receptor blockers, calcium channel blockers. The study was initiated after it was approved by both the Ministry of Health and ethics board of Bezmialem Vakıf University.

Doppler US method: The patients were instructed to fast after midnight and the analysis was performed between 09-12 a.m. Logiq 9 (GE, Milwaukee, USA) US and 3.5 MHz convex probe were used for the analysis when the patient was lying on left lateral decubitus position. First, all liver segments were examined on gray scale and presence and degree of hepatosteatosis were recorded. PV measurements were performed on portal confluence. Doppler degree was maintained at 30°-60°. Appropriate Doppler gain and filter adjustments were made. PV spectrum was recorded for at least 5 seconds mid-inspiration and measurements were made over this wave pattern. PV diameter, flow pattern, flow velocity and flow volume were assessed. These parameters were measured three times for each patient and the mean of measurements was taken.

Venous blood samples were obtained from the patients at least 10-12 hours of fasting. Patients' blood samples were used to measure the following laboratory values: HbA_{1c} (turbidimetric inhibition immunoassay; Roche), low-density lipoprotein cholesterol (LDL-C), triglyceride, hemogram, and alanine aminotransferase (ALT) and creatinine values (immunoassay chemiluminescent method; Beckman Coulter, Pasadena, CA, USA).

Statistical Analysis

SPSS (Statistical Package for Social Sciences) for Windows 15.0 software was used in statistical analyses.

During the assessment of study findings, Student's t-test and paired-samples t test were used to compare parameters with normal distribution. Mann-Whitney U test and Wilcoxon were used to compare parameters without normal distribution. Chi-square and marginal homogeneity tests were employed to compare the proportional data. A two-sided p value of <0.05 was considered significant.

Results

The study was initiated with 48 patients with type 2 DM in the vildagliptin group. After 18 months of follow-up, and the study was completed with 19 participants, 5 of whom were male. On the other hand, the control group including the subjects who did not receive vildagliptin started the study with 49 patients with

type 2 DM. This group completed the study with 10 subjects, 5 of whom were male. Demographics and laboratory values of subjects who were treated with vildagliptin did not differ significantly from those of the subjects in the control group. Pre- and post-treatment demographics and laboratory values of subjects in the vildagliptin group were mostly comparable. There was, however, a significant decrease in the creatinine level ($p=0.02$) and a significant increase in ALT level ($p=0.02$) (Table 1). Pre- and post-treatment values in the control group did not differ significantly (Table 2).

PV flow velocity, PV flow volume and PV diameter were measured with doppler US in the control and the vildagliptin groups. Comparison of PV parameters in the vildagliptin group demonstrated significant increases in terms of PV flow velocity and PV diameter ($p<0.001$, $p=0.035$, respectively). No significant difference was observed for PV flow volume. In the control group, no significant differences were seen for PV flow velocity or PV flow volume, although there was a significant increase in the PV diameter (Table 3). Comparison of 18-month therapy results between the vildagliptin group and the control group demonstrated no significant differences in the PV flow velocity, PV flow volume or diameter ($p=0.66$, $p=0.2$, $p=0.67$, respectively).

Assessment of hepatosteatosis grades did not demonstrate any significant increases in terms of steatosis ($p=0.157$). There was

Table 1. The demographic and laboratory characteristics of the subjects by groups

	Pre vildagliptin (n=19)	Post vildagliptin (n=19)	<i>p</i>
Age (years)	52.16±7.18		
BMI (Kg/m ²)	33.3±5.5	33.16±4.9	0.72
Glucose (mg/dL)	160.5±37	155.5±33.8	0.58
HbA _{1c} (%)	7.16±1.08	7.02±1	0.8
Creatinine (mg/dL)	0.75±0.14	0.62±0.14	0.02
ALT (U/L)	23.6±8.5	31.9±13.9	0.02
LDL-C (mg/dL)	127.8±40.3	121.8±61	0.39
Triglyceride (mg/dL)	153±60	148±24.4	0.98

Vildagliptin group: Subjects on metformin, gliclazide and vildagliptin, HbA_{1c}: Hemoglobin A_{1c}, ALT: Alanine aminotransferase, LDL-C: Low-density lipoprotein-cholesterol, BMI: Body mass index

Table 2. The demographic and laboratory characteristics of the subjects by groups

	Pre control (n=10)	Post control (n=10)	<i>p</i>
Age (years)	55.4±9.2		
BMI (Kg/m ²)	30.8±6.3	30.6±4.8	0.8
Glucose (mg/dL)	149.8±19.6	156.8±35.3	0.7
HbA _{1c} (%)	6.75±0.5	6.95±0.39	0.58
Creatinine (mg/dL)	0.83±0.15	0.68±0.08	0.07
ALT (U/L)	16.5±5.3	27.7±4.3	0.09
LDL-C (mg/dL)	124.3±42.2	134.3±38.9	0.08
Triglyceride (mg/dL)	106.3±41	130.3±116	0.6

Control group: Subjects on metformin and gliclazide, HbA_{1c}: Hemoglobin A_{1c}, ALT: Alanine aminotransferase, LDL-C: Low-density lipoprotein cholesterol, BMI: Body mass index

Table 3. Portal vein flow velocity, portal vein flow volume, and portal vein diameter by group

	Pre vildagliptin (n=19)	Post vildagliptin (n=19)	<i>p</i>	Pre control (n=10)	Post control (n=10)	<i>p</i>
Portal vein flow velocity (L/min)	7.8±1.2	15.4±5.6	<0.001	8.4±2.3	9.5±2.25	0.07
Portal vein flow volume (cm/s)	475±145	428±182	0.44	488±95	599±139	0.14
Portal vein diameter (mm)	11.77±1.8	12.83±1.9	0.035	11.04±1.37	12.5±1.14	0.04

Vildagliptin group: Subjects on metformin, gliclazide and vildagliptin, Control group: Subjects on metformin and gliclazide

Table 4. Comparison of steatosis grades with ultrasonography between groups in pre- and post-treatment periods

Grade	Pre vildagliptin (n=19)	Post vildagliptin (n=19)	p	Pre control (n=10)	Post control (n=10)	p
Grade 0-1	10	8	0.157	6	8	0.157
Grade 2-3	9	11		4	2	

Vildagliptin group: Subjects on metformin, gliclazide, and vildagliptin, Control group: Subjects on metformin and gliclazide

no significant increase between the control and vildagliptin groups in terms of hepatosteatosis after 18 months of treatment (Table 4).

Vildagliptin and control groups' pre- and post-treatment white blood cell, hemoglobin, hemotocrit, mean corpuscular volume and platelet values did not differ significantly ($p=0.98$, $p=0.53$, $p=0.35$, $p=0.38$, $p=0.29$, $p=0.39$, $p=0.94$, $p=0.7$, $p=0.27$, $p=0.7$, respectively).

Power analysis calculation of the study based on PV flow velocity yielded a value of 98% in the vildagliptin group.

Discussion

DPP-4 inhibitors are demonstrated to reduce glucose and glucagon levels by increasing serum levels of GLP-1 and GIP hormones. These hormones are known to potentiate NO release by acting on the endothelia in several tissues (6). It is recognized that elevated levels of NO induce vasodilation in the PV, whereas decreased levels of glucagon are known to cause vasodilation in the splenic vein. In addition to these data, DPP-4 activity was found to be increased in patients with non-alcoholic hepatosteatosis, and hepatosteatosis grade was found to be higher with increasing levels of DPP-4 (8). Vildagliptin is a DPP-4 inhibitor which is recommended rarely in patients at risk of asymptomatic hepatitis, because its prescribing information advises hepatic function monitoring four times yearly. Based on these data, a decrease in PV pressure and increase in hepatic steatosis may be expected with short- and long-term vildagliptin use. In our study, we intended to investigate these potential effects of vildagliptin using non-invasive methods.

Significant increase in PV flow velocity and PV diameter was observed in subjects using vildagliptin in our study. These may be interpreted as a non-invasive indicator of reduced PV pressure (9). In vildagliptin users, increased PV diameter may be expected as a consequence of increased NO levels. There was no significant decrease in PV flow volume.

Reduced PV flow volume is recognized as an indicator of reduced PV pressure. Cell culture studies showed that exogenous GIP given to dog fetal cell culture increased NO release from PV (4). We could not identify any studies investigating the effect of DPP-4 inhibitors on NO in portal veins. There are, however, many studies on other tissues and organs. In one of these, obese rats were treated with saxagliptin and aortic and glomerular endothelial NO levels were measured. The authors showed significantly elevated endothelial NO levels in animals treated with saxagliptin (10). Another study demonstrated decreased

levels of serum acetyl di-methyl arginine, which is recognized as an indirect indicator of NO elevations, in subjects receiving vildagliptin (11). These results may be supportive of the results obtained in our study. On the other hand, significantly increased PV diameter in the control group was not, in fact, an expected outcome. Absence of a significant difference in PV flow volume and PV flow velocity may indicate that PV pressure was not significantly affected. Vildagliptin seems to cause a reduction in PV pressure when the results obtained from the vildagliptin group and the control group were taken separately. However, when we compared the 18-month differences of the vildagliptin and control groups, we determined that PV parameters were all comparable between the groups. This contradiction may be explained as follows: although these parameters seemed to differ significantly when assessed in individual groups, the difference, in fact, was very small and when the whole sample was evaluated, the difference was not significant. These results may suggest that the parameters which allowed indirect estimation of PV pressure were not altered to a significant extent with vildagliptin use.

Patients who completed the 18-month 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 reported that DPP-4 inhibitors corrected hepatic steatosis as well as those which described a close association with hepatic steatosis (12). 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 (13). Another study reported increased hepatosteatosis with increasing levels of DPP-4 (8). Our results did not indicate a significant increase in hepatic steatosis.

Another important outcome of the study was that there was a statistically significant decrease in serum creatinine levels in patients receiving vildagliptin versus no significant difference in the creatinine levels in the control group. A previous study found significantly reduced levels of urinary albumin creatinine in subjects who used vildagliptin for 8 weeks compared to controls (14). Another study demonstrated a significant decrease in creatinine levels in rats treated with vildagliptin (15). The results of these studies are consistent with the results of our study.

The limitation of our study was that we did not measure the hepatic venous pressure gradient with the invasive angiography, the golden standard of assessing PV pressure. Instead, we preferred portal doppler US which is a non-invasive method and is efficient in determining the severity of portal hypertension.

PV flow velocity, diameter and flow volume measured with PV doppler US was reported to have a sensitivity and specificity of 80% in reflecting PV pressure (16,17). Another limitation was that a low number of patients completed 18-month treatment in the study.

In conclusion, satisfactory evidence to suggest that vildagliptin use results in a significant decrease in PV pressure was not obtained. However, these results may suggest that vildagliptin does not increase PV pressure. This may be particularly important when selecting an agent for patients with PV pressure. It should also be kept in mind that increased NO release can be dangerous in patients who have esophageal varices or are at risk of having bleeding in esophageal varices. As the second outcome of the study, vildagliptin was not shown to have an effect on hepatosteatosis. This requires larger studies. Further studies are also needed to elucidate whether the obtained results are associated with vildagliptin or are class effects of DPP-4 inhibitors.

Ethics

Ethics Committee Approval: The study was initiated after it was approved by both the Ministry of Health and ethics board of Bezmailem Vakıf University.

Informed Consent: Written consent was obtained from the students who agreed to participate in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: C.K., Design: C.K., Data Collection or Processing: M.Z., M.K., Analysis or Interpretation: C.K., Writing: C.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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