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Original Article

Retrospective Evaluation of Microalbuminuria and GFR Levels of Diabetic Patients Taking DPP-4 Inhibitor, GLP-1 Analog, or SGLT-2 Inhibitor

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ABSTRACT

Background In our study, we determined the changes in microalbuminuria and GFR (glomerular filtration rate) values, which are important for diabetic nephropathy, within 1 year after starting treatment in our patients taking DPP-4 inhibitor (linagliptin), GLP-1 analog (exenatide) and SGLT-2 inhibitor (empagliflozin).

Material and Methods We evaluated the urea, creatinine, gfr and microalbuminuria levels of our patients who were treated with linagliptin, exenatide and empagliflozin on their 0th, 6th and 12th month visits. We included patients who were followed up for nephropathy for at least 1 year after starting treatment in each drug group.

Results When the 0th and 12th month GFR values of our 98 patients who were prescribed linagliptin were compared, an increase of 4.57% was detected ($p<0.01$). In this group, there were 55 patients whose microalbuminuria could be followed up at 12 months, and no significant change was detected ($p>0.05$). While no statistically significant difference was found in the 0th and 12th month GFR follow-ups of our 97 patients using exenatide ($p>0.05$); in this group, it was determined that the microalbuminuria decreased significantly in 12 months in 33 of our patients who could be followed up in terms of microalbuminuria ($p<0.05$). No statistically significant change was observed in the 0th and 12th month GFR follow-ups of our 99 patients taking empagliflozin ($p>0.05$); however, it was determined that microalbuminuria decreased significantly at the end of 1 year in our 79 patients who could be followed up for microalbuminuria in this group ($p<0.05$).

Conclusions Although there was no improvement in microalbuminuria in our patients taking linagliptin, an increase in GFR was observed; however, it was observed that this situation was associated with the discontinuation of the nephrotoxic agents used by the patients for the treatment of diabetes and switching to linagliptin. In our patients taking exenatide and empagliflozin, although no significant change was detected in the GFR value, a decrease in microalbuminuria was observed; this is important in order to prevent the progression of nephropathy in the early period. The results of our study suggest that the use of GLP-1 analog and SGLT-2 inhibitor in diabetic patients will provide a nephroprotective effect.

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Introduction

Diabetes mellitus is one of the most important causes of chronic kidney disease and end-stage renal disease worldwide.[1] Although it is thought that diabetic nephropathy classically starts with albuminuria (≥30 mg/day or ≥20 μg/minute or ≥30 μg/mg creatinine) that develops after diabetic retinopathy, some studies show that the estimated glomerular filtration rate (eGFR) may decrease even before albuminuria develops.[2] Thus, despite the limitations of "albuminuria as the earliest marker" of diabetic nephropathy, many scientists suggest that rapid eGFR decline is of prognostic importance.[3] Some patients with diabetes mellitus paradoxically have a high GFR early in the course of the disease, and this is called "glomerular hyperfiltration". Glomerular hyperfiltration has been associated with the risk of progression of albuminuria and impaired renal function.[4,5] High albuminuria levels and low eGFR in patients with diabetic nephropathy independently and additionally increase the risk of cardiovascular complications and death.[6-10] In this study, we retrospectively analyzed the changes in microalbuminuria and gfr levels in our patients taking DPP-4 (dipeptidyl peptidase 4) inhibitor, GLP-1 (glucagon like peptide 1) analog or SGLT-2 (sodium glucose cotransporter 2) inhibitor.

Material and Methods

The study was conducted after the approval of the local ethics committee in accordance with the Helsinki Declaration. In this retrospective study, patients who were started on linagliptin (DPP-4 inhibitor), exenatide (GLP-1 analog) or empagliflozin (SGLT-2 inhibitor) and continued for at least 12 months; changes in albuminuria and glomerular filtration rate levels were investigated before, 6 months after and 1 year after starting to take these medications. Adult (>18 years old) patients diagnosed with type 2 diabetes mellitus; patients who had been taking DPP-4 inhibitor, GLP-1 analog or SGLT-2 inhibitor for at least 12 months and patients with full hospital controls were included in the study. Patients with type 1 diabetes mellitus, those in the pediatric age group, women in pregnancy and lactation period, and patients whose hospital controls were missing after the medications was prescribed were excluded from the study. In total, the files of 546 patients were reviewed retrospectively (229 linagliptin, 140 exenatide, and 177 empagliflozin), and 100 patients from each drug group who met the criteria were included in the study and the data of 300 patients were analyzed. Age and gender distribution, changes in albuminuria and gfr levels at 0th, 6th and 12th months of treatment were evaluated in all three treatment groups.

Statistical Analysis

The conformity of continuous variables to the normal distribution was examined using the Shapiro-Wilk test. Variables are expressed as mean±standard deviation, median (minimum:maximum) or n (%). The Kruskal-Wallis test was used for comparisons between treatment groups according to the results of the normality test. In case of significance after the Kruskal-Wallis test, pairwise comparisons between the groups were made using Dunn's test. The Wilcoxon Signed Rank test or the t-test for paired samples were used in the analyses performed to compare the measurements obtained at the 6th and 12th months with the baseline values in the treatment groups. Intergroup comparisons of categorical variables were performed using Pearson's chi-square test, Fisher-Freeman-Halton test, or Fisher's exact chi-square test. All statistical analyses were performed using IBM SPSS Statistics version 21.0 and a p-value of 0.05 was considered statistically significant.

Results

The mean age was 62.19±12.02 years in our patients taking linagliptin, 56.23±10.76 years in patients taking exenatide, and 58.20±10.31 years in patients taking empagliflozin. There was a significant difference between the treatment groups according to age distribution. In subgroup analyses, the median age was found to be higher in patients taking linagliptin than in the exenatide and empagliflozin groups ($p<0.001$ and $p=0.026$, respectively) (*Table 1*). Gender ratio were 49% female in the linagliptin group, 81% in the exenatide group and 57% in the empagliflozin group ($p<0.001$) (*Table 1*).

Table 1. Comparison of age and gender between treatment groups.

	Linagliptin (n=100)	Exenatide (n=100)	Empagliflozin (n=100)	p value	Binary comparisons (group I vs group J)		
					PLin-Exe	PLin-Empag	PExe-Empag
Age (years)	64 (22:90) 62.19±12.02	57 (29:77) 56.23±10.76	59 (28:79) 58.20±10.31	<0.001[a]	<0.001[d]	0.026[d]	>0.999[d]
Gender							
Female	49 (49%)	81 (81%)	57 (57%)	<0.001[b]	<0.001[b]	0.257[b]	<0.001[b]
Male	51 (51%)	19 (19%)	43 (43%)				

Data were given as n (%), median (minimum:maximum) and mean±standard deviation.
a: Kruskal-Wallis Test, b: Pearson Chi-Square test, c: Fisher-Freeman-Halton test, d: Dunn test.

The median value of urea measurements in patients who were prescribed linagliptin treatment was 43.50 (12:115) mg/dL at 0 month, 39 (12:142) mg/dL at 6 month, and 38.50 (16:192) mg/dL at 12 month. In comparisons made with reference to month, no significant difference was found in terms of urea value at 6th month and 12th month (p=0.397 and p=0.660). The median value of creatinine measurements at 0th month was 1.03 (0.48:3.80) mg/dL, 1.09 (0.45:4.30) mg/dL at 6th month, and 1 (0.48:5.50) mg/dL at 12th month. In comparisons made with reference to month 0, no significant difference was found in terms of creatinine value at 6th and 12th months (p=0.897 and p=0.191). The median value of albuminuria level at 0 month was 51 (5:2,600) mg/day, 43.50 (5:2,100) mg/day at 6th month and 55.50 (6:2,597) mg/day at 12th month. In comparisons made with reference to month 0, no significant difference was found in terms of albuminuria level at 6th and 12th months (p= 0.833 and p=0.406). The median values of GFR measurements were 62 (12:123) mL/min/1.73 m^2 at 0th month, 65 (10:130) mL/min/1.73 m^2 at 6th month, and 64 (8:126) mL/min/1.73 m^2 at 12th month. In comparisons made with reference to month 0, it was observed that there was no significant change in GFR at 6th month (p=0.094), but there was an increase of 3.23% at the end of 12th month (p<0.01) (*Table 2*).

The median value of urea measurements in patients who were prescribed on exenatide treatment was found to be 28 (9:83) mg/dL at 0th month, 31(12:54) mg/dL at 6th month, and 28 (0.74:71) mg/dL at 12th month. In comparisons made with reference to month 0, no significant difference was found in terms of urea value at 6th and 12th months (p=0.365 and p=0.455). The median value of creatinine measurements at 0th month was 0.75 (0.55:1.76) mg/dL, 0.77 (0.53:1.57) mg/dL at 6th month, and 0.76 (0.57:1.87) mg/dL at 12th month. In comparisons made with reference to month 0, no significant difference was found in terms of creatinine value at 6th and 12th month (p=0.999 and p=0.277). The median value of albuminuria level at 0th month was 19.50 (6:995) mg/day, 18.50 (6:1643) mg/day at 6th month and 16 (5:1681) mg/day at 12th month. In comparisons made with reference to month 0, no significant difference was found in terms of albuminuria level at 6th month (p=0.789). At 12th month, a decrease of 17.95% was detected compared to the baseline (p=0.024). The mean of GFR measurements were 87.78±17.65 mL/min/1.73 m^2 at 0th month, 87.76±16 mL/min/1.73 m^2 at 6th month, and 88.57±15.24 mL/min/1.73 m^2 at 12th month. In comparisons made with reference to month 0, no significant difference was found in terms of GFR values at 6th and 12th months (p=0.623 and p=0.536) (*Table 3*).

The mean urea level of the patients who were prescribed empagliflozin treatment was 31.28±9.74 mg/dL at 0th month, 33.44±11.91 mg/dL at 6th month, and 33.89±17.71 mg/dL at 12th month. In comparisons made with reference to month 0, an increase of 6.91% was observed at month 6 (p=0.031). At the 12th month, no significant difference was found in terms of urea value compared to the baseline (p=0.098). The median values of creatinine measurements at month 0 were 0.79 (0.56:1.17) mg/dL, 0.79 (0.45:1.50) mg/dL at 6th month, and 0.80 (0.54:4.30) mg/dL at 12th month. In comparisons made with

Table 2. Comparisons for the linagliptin treatment group.

	Descriptive statistics	PC%	p value
Urea (mg/dL)			
Beginning (n=89) → 6th month (n=89)	43.50 (12:115) → 39 (12:142)	↓10.34%	0.397[e]
Beginning (n=98) → 12th month (n=98)	43.50 (12:115) → 38.50 (16:192)	↓11.49%	0.660[e]
Creatinine (mg/dL)			
Beginning (n=89) → 6th month (n=89)	1.03 (0.48:3.80) → 1.09 (0.45:4.30)	↑5.83%	0.897[e]
Beginning (n=98) → 12th month (n=98)	1.03 (0.48:3.80) → 1 (0.48:5.50)	↓2.91%	0.191[e]
GFR (mL/min/1.73 m^2)			
Beginning (n=89) → 6th month (n=89)	62 (12:123) → 65 (10:130)	↑4.84%	0.094[e]
Beginning (n=98) → 12th month (n=98)	62 (12:123) → 64 (8:126)	↑3.23%	<0.001[e]
Microalbuminuria (mg/day)			
Beginning (n=24) → 6th month (n=24)	51 (5:2,600) → 43.50 (5:2,100)	↓14.71%	0.833[e]
Beginning (n=30) → 12th month (n=30)	51 (5:2,600) → 55.50 (6:2,597)	↑8.82%	0.406[e]

Data were given as median (minimum:maximum) and mean±standard deviation.
PC: percentage change in mean or median, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GFR: glomerular filtration rate, e: Wilcoxon Signed Rank, f: t-test for paired samples.

Table 3. Comparisons for the exenatide treatment group.

	Descriptive statistics	PC%	p value
Urea (mg/dL)			
Beginning (n=91) → 6th month (n=91)	28 (9:83) → 31 (12:54)	↑10.71%	0.365[e]
Beginning (n=98) → 12th month (n=98)	28 (9:83) → 28 (0.74:71)	0%	0.455[e]
Creatinine (mg/dL)			
Beginning (n=90) → 6th month (n=90)	0.75 (0.55:1.76) → 0.77 (0.53:1.57)	↑2.67%	>0.999[e]
Beginning (n=98) → 12th month (n=98)	0.75 (0.55:1.76) → 0.76 (0.57:1.87)	↑1.33%	0.277[e]
GFR (mL/min/1.73 m^2)			
Beginning (n=91) → 6th month (n=91)	87.78±17.65 → 87.76±16	↓0.02%	0.623[f]
Beginning (n=97) → 12th month (n=97)	87.78±17.65 → 88.57±15.24	↑0.9%	0.536[f]
Microalbuminuria (mg/day)			
Beginning (n=12) → 6th month (n=12)	19.50 (6:995) → 18.50 (6:1643)	↓5.13%	0.789[e]
Beginning (n=33) → 12th month (n=33)	19.50 (6:995) → 16 (5:1681)	↓17.95%	0.024[e]

Data were given as median (minimum:maximum) and mean±standard deviation.
PC: percentage change in mean or median, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GFR: glomerular filtration rate, e: Wilcoxon Signed Rank, f: t-test for paired samples.

Table 4. Comparisons for the empagliflozin treatment group.

	Descriptive statistics	PC%	p value
Urea (mg/dL)			
Beginning (n=97) → 6th month (n=97)	31.28±9.74 → 33.44±11.91	↑6.91%	0.031[f]
Beginning (n=99) → 12th month (n=99)	31.28±9.74 → 33.89±17.71	↑8.34%	0.098[f]
Creatinine (mg/dL)			
Beginning (n=97) → 6th month (n=97)	0.79 (0.56:1.17) → 0.79 (0.45:1.50)	0%	0.681[e]
Beginning (n=99) → 12th month (n=99)	0.79 (0.56:1.17) → 0.80 (0.54:4.30)	↑1.27%	0.493[e]
GFR (mL/min/1.73 m^2)			
Beginning (n=97) → 6th month (n=97)	89.40±14.47 → 89.19±15.85	↓0.23%	0.577[f]
Beginning (n=99) → 12th month (n=99)	89.40±14.47 → 89.14±15.78	↓0.29%	0.567[f]
Microalbuminuria (mg/day)			
Beginning (n=52) → 6th month (n=52)	52.57±129.63 → 22.32±18.82	↓57.54%	0.052[f]
Beginning (n=79) → 12th month (n=79)	52.57±129.63 → 27.39±53.31	↓47.9%	0.027[f]

Data were given as median (minimum:maximum) and mean±standard deviation.
PC: Percentage change in mean or median, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GFR: glomerular filtration rate, e: Wilcoxon Signed Rank, f: t-test for paired samples.

reference to month 0, no significant difference was found in terms of creatinine value at 6th and 12th months (p=0.681 and p=0.493). The mean level of albuminuria at 0th month was 52.57±129.63 mg/day, at 6th month 22.32±18.82 mg/day, and at 12th month 27.39±53.31 mg/day. In comparisons made with reference to month 0, no significant difference was found in terms of albuminuria level at 6th month (p=0.052). There was a 47.9% decrease from the baseline at 12th month (p=0.027). The mean of GFR measurements were 89.40±14.47 mL/min/1.73 m^2 at 0th month, 89.19±15.85 mL/min/1.73 m^2 at 6th month, and 89.14±15.78 mL/min/1.73 m^2 at 12th month. In comparisons made with reference to month 0, no significant difference was found in terms of GFR values at 6th and 12th months (p=0.577 and p=0.567) (*Table 4*).

Discussion

When the previous studies on the renal effects of linagliptin, exenatide and empagliflozin treatments that we examined in our study were scanned, it was seen that the age range was 55-65 years.[11-20] It was determined that the mean age of patients taking linagliptin, which we included in the study, was 64, 57 in patients taking exenatide, and 59 in patients taking empagliflozin; this was in agreement with the literature.

While the gender distribution was consistent with the literature in patients taking linagliptin and empagliflozin, the proportion of female patients taking exenatide was higher than the literature. The reason for this is thought to be due to the fact that exenatide treatment can be started in diabetic patients with a body mass index >35 kg/m^2 in accordance with the SUT (health practices communiqué) and obesity is more common in women in Turkey.[21] In studies on DPP-4 inhibitors, SGLT-2 inhibitors or GLP-1 analogues, the rate of female patients was found to be around 35-45%.[12-16,19,22,23] In our study, the rate of female patients was 81% in the exenatide group.

While there was no significant change in

microalbuminuria, urea and creatinine values in our patients taking linagliptin, GFR increased by 3.23% at the end of one year. It is known that linagliptin has no renoprotective effect.[22] However, it is thought that this situation may be related to the discontinuation of the nephrotoxic diabetes treatment of the patients and switching to linagliptin, which has no nephrotoxic effect.

In our study, it was observed that there was no significant change in urea, creatinine and GFR levels in the patient group taking exenatide, and no GFR change was observed in other studies.[24,25] In the EXSCEL study, no significant change was found in the amount of albuminuria, but in our study, it was determined that the microalbuminuria level decreased by 7.95% at the end of one year after the treatment was started. In a study conducted in Croatia in 2016, it was observed that exenatide treatment in obese type 2 diabetes patients significantly reduced the amount of albuminuria 22 months after starting treatment.[26]

In the patient group taking empaglifilozin, no significant changes were detected in urea, creatinine and GFR levels during the 1-year follow-up. In the twelfth month of the treatment, a 47.9% decrease was observed in the microalbuminuria level. This is related to the renoprotective effect of SGLT-2 inhibitors.[27]

Conclusions

Our aim in conducting this study was to show the real-life projection of large studies and to see how much we could protect our patients who started taking SGLT-2 inhibitor or GLP-1 analogue from renal pathologies. As a result, we have seen that we can better protect patients who use GLP-1 analog and SGLT-2 inhibitor from albuminuria, which gives information about the prognosis of diabetic nephropathy. There are studies with different results in the literature with the renoprotective effects of DPP-4 inhibitors; therefore, there is a need for new studies on this drug group that have been tried in a larger patient group.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: BG; Study Design: OOG, SC; Supervision: OOG, SC; Materials: BG; Data Collection and/or Processing: BG; Statistical Analysis and/or Data Interpretation: BG, OOG, SC; Literature Review: BG, OOG, SC; Manuscript Preparation: BG, OOG, SC; Critical Review: OOG, SC.

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