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Research Article

Amelioration of Albuminuria by Sitagliptin Added to Metformin in Patients with Type 2 Diabetes and Incipient Nephropathy: A Real World Data Study

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Abstract

Clinical trials have demonstrated that in patients with type 2 diabetes (T2DM) and albuminuria, dipeptidyl peptidase 4 inhibitors (DPP-4i) are associated with urine albumin-to-creatinine ratio (UACR) reduction. We examined whether a similar effect is observed in clinical practice. Using the electronic medical database of a 2-million-member health organization, we identified 1,248 individuals with T2DM and albuminuria who had sitagliptin added to metformin for a period of at least 120 days. Patients were divided into categories according to baseline UACR: 30-300 mg/g (81%, n=1011) and > 300 mg/g (19%, n=237). All patients had a second UACR obtained following 60 days or more of treatment with sitagliptin. Sitagliptin therapy led to a reduction in HbA1c (-0.69%; -16 mmol/mol p < 0.001) and was significantly associated with a reduction of UACR [median reduction of 31.8% (23.3mg/g) p < 0.001]. In 403 (32.3% of) patients the change in UACR represents a shift to a lower UACR category, while 55 (4.4%) patients shifted to a higher UACR category. Although UACR change was associated with a change in HbA1c (r=0.208, p < 0.001) UACR also significantly decreased for patients without a reduction in HbA1c. In a multivariable model, a baseline UACR of > 300 mg/g Cr in sitagliptin treated patients was associated with an OR of 1.46(95% CI 1.08-1.98) for having a reduction in UACR category compared patients with a UACR of 30-300 mg/g. Males, obese patients, patients with lower eGFR and patients with hypertension were less likely to have a reduction in UACR category. This observational study indicates that sitagliptin added to metformin may decrease UACR in most patients with T2DM and incipient nephropathy in clinical practice, independent of its effect on HbA1c. Whether this represents a glucose-independent DPP-4 mechanism needs further study.

ABBREVIATIONS

T2DM: Type 2 Diabetes; DPP-4i: Dipeptidyl Peptidase 4 Inhibitors; UACR: Urinary Albumin/Creatinine Ratio; GLP-1: Glucagon-Like Peptide-1; MHS: Maccabi Health Services; HMO: Health Maintenance Organization; eGFR: Estimated Glomerular Filtration Rate; BMI: Body Mass Index; ACEi: Angiotensin-I-Converting Enzyme Inhibitor; ARB: Angiotensin-II-Receptor Blocker; SES: Socioeconomic Status.

INTRODUCTION

Diabetic nephropathy is a progressive disease. Hyperglycemia and hypertension are the main drivers of advancement toward renal failure [1]. Slowing of disease progression can be achieved through intensive efforts to manage blood glucose and blood pressure. Nevertheless, new treatment paradigms are needed to address the failure to prevent end stage renal disease with current therapies.

Incretin-based therapies have rapidly gained recognition as a key component of the therapeutic armamentarium by the American Diabetes Association [2,3]. Dipeptidyl peptidase 4 inhibitors (DPP-4i) are oral antihyperglycaemic agents that prevent the rapid degradation of glucagon-like peptide-1(GLP-1). Preclinical evidence suggests that DPP4i may be beneficial in cases of acute renal failure and chronic kidney diseases such as diabetic nephropathy [4,5]. There is good evidence that both GLP-1 receptors and DPP-4i are present in the renal tubules although

the mechanism of their effect on renal function is still unclear [6].

Increased urinary excretion of albumin reflects kidney damage and is a recognized risk factor for progression of renal disease [1,6-7]. In addition to being the earliest indicators of nephropathy, macro- and microalbuminuria are also predictive risk factors for non-fatal and fatal cardiovascular events in patients with and without diabetes. Decreased rates of morbidity and mortality have been observed with therapeutic interventions that are associated with reductions in albumin excretion [6,8-12].

Recent clinical trials have demonstrated that DPP-4i may decrease UACR, the accepted parameter for quantification of albumin excretion in patients with T2DM [12-16]. Although this effect may be generalized to several glucose lowering classes of drugs, these observations along with pre-clinical data may suggest a potential reno-protective effect of DPP-4i beyond its glucose-lowering potential [6,17].

Maccabi Health Services (MHS) runs a diabetes registry of central electronic medical record that holds information on both sitagliptin use as well as urinary albumin excretion, thus allowing for the evaluation of sitagliptin effectiveness on urinary albumin excretion and progression of renal disease in clinical practice. The objective of this study was to describe the effect of sitagliptin treatment on urinary albumin excretion in patients with T2DM.

MATERIALS AND METHODS

This retrospective cohort study was based on the computerized database of MHS, a large Israeli Health Maintenance Organization (HMO) serving 2 million members. The study was approved by the MHS internal review board.

All patients with T2DM ever treated with sitagliptin from July 1st 2007 to January 31th 2013 (first sitagliptin purchase was defined as the index date) were screened (> 25,608 patients). Inclusion criteria were: a. ≥ 120 days of continuous sitagliptin purchases during 180 calendar days; b. an UACR test result > 30 mg/g Cr during a 4 month period prior to the index date (baseline period) and a second UACR measurement after ≥ 60 days from the index date while on sitagliptin treatment; c. metformin purchases for ≥ 60 days during 90 days prior to the index date; and d. baseline estimated glomerular filtration rate (eGFR) > 45 ml/min/1.73m^2. Excluded were individuals with less than 18 months of membership in MHS (n=771) or on dialysis (n=39). There were no pregnant women in the study cohort. We also recorded data regarding age, sex, body mass index (BMI) and angiotensin-I-converting enzyme inhibitors (ACEi) or angiotensin-II-receptor blocker (ARB) and non-steroidal anti-inflammatory drugs (NSAIDs) use.

Two HbA1c measurements were recorded: baseline measurement was the last HbA1c measurement obtained within 4 months prior to the index date; a second HbA1c measurement was defined as the first HbA1c measurement ≥ 90 days from the index date and while on sitagliptin treatment. Treatment with ACEi/ ARB or with NSAIDs was defined as having at least 1 dispense within 90 days prior to each UACR measurement.

In some cases, UACR values > 300 mg/g Cr were reported only as a remark and the exact numeric value was not available (208 patients). These patients were excluded from analyses using UACR absolute or percent change.

STATISTICAL ANALYSIS

Data were reported as a mean [standard deviation (SD)] for continuous variables and as numbers of patients and percentages for categorical variables. P-values were calculated by Wilcoxon sum rank test and Kruskal-Wallis test for comparisons of two categories and more than two categories, respectively or by the Wilcoxon signed Rank test.

T test was used for continuous variables. Correlation between variables was examined by Pearson correlation.

A logistic regression model was calculated to estimate factors influencing the probability of having a reduction in UACR category (i.e., moving to a later category at follow-up from a previous category at baseline in the following order: macro-albuminuria/ micro- albuminuria/ normo- albuminuria). Covariates entered into the model were age (< 65 or ≥ 65) at the index date, gender, level of socioeconomic status (SES, categorized into ten levels according to the poverty index of the member's enumeration area as defined by the 2008 national census based on household income, education level, crowding, material conditions and car ownership), included in hypertension registry and baseline measures of the following: obesity (BMI < 30kg/m2 or ≥ 30 kg/m2), UACR (30-300 and > 300 mg/g Cr), HbA1c (≤ 8% and > 8%, ≤ 64 and > 64 mmol/mol), eGFR (45-60 ml/min/1.73m^2 and > 60 ml/min/1.73m^2) and ACEi/ARB use.

Analyses were conducted using SAS version 9.2 for Windows (SAS Institute, Cary, NC).

RESULTS AND DISCUSSION

Results

1,248 patients were included in the analysis. The characteristics of these patients are presented in (Table 1). Briefly, mean age was 62.5 years (SD=10.0) and 834 (66.8%) were males. Mean (SD) BMI was 31.7 kg/m2 (1.4 kg/m2) and mean (SD) HbA1c was 8.2%; 66 mmol/mol (1.4%; 8 mmol/mol). A total of 81% and 19% of the study population had a baseline UACR of 30-300 and > 300 mg/g Cr, respectively. During the baseline period, 83.2 % of the study population purchased ACE-i or ARB. Among 971 hypertensive patients, 906 of them (93.3%) were treated with statins or fibrates. Mean treatment time on sitagliptin was 871(Min-Max: 123-1993 days, SD 460) days. Mean time between the two UACR measurements was 228 (SD 171) days, and between the two HbA1c determinations was 203 (SD 114) days. Mean HbA1c level decreased by 0.69% (16 mmol/mol(1.29 SD)) from baseline (P < 0.001) and 364 (29.2%) patients achieved > 1% (13 mmol/mol) reduction in HbA1c.

Sitagliptin therapy was associated with a reduction in UACR [median reduction of 31.8% from baseline (23.25mg/g Cr) p < 0.001]. Four hundred and three patients (32.3%) shifted to a lower UACR category, while only 55 patients (4.4%) shifted to a higher category. Figure 1 depicts the shift between the various UACR categories compared to baseline UACR category (P < 0.001).

Sitagliptin therapy led to a reduction of UACR in all baseline HbA1c categories (Table 2). Change in UACR was correlated to the

Baseline UACR (mg/g Creatinine)	Second UACR (mg/g Creatinine) Measurement					
	<=30		30-300		>300	
	n	%	n	%	n	%
30-300	314	31.1	642	63.5	55	5.4
>300	11	4.6	78	32.9	148	62.4

Decrease in UACR by one category (mild improvement of proteinuria)

Decrease in UACR by two categories (moderate improvement of proteinuria)

Remained in the same UACR category (no change in proteinuria)

Increase in UACR by one category (mild worsening of proteinuria)

Figure 1 Shift of UACR (mg/g creatinine) measurements.

change in HbA1c (r=0.208, p < 0.001) while baseline HbA1c was not correlated to change in UACR. Females, patients with lower BMI, higher reduction in HbA1c and who started treatment with ACEi/ARB after the index date showed more reduction in UACR. A sub-analysis after excluding patients who initiated treatment with ACEi/ARB agents found UACR decreased by a median of 28.8% (P < 0.001). Among elder patients (120 patients age ≥ 75), there was no significant difference in change in UACR by change in NSAIDs before UACR measurements (median (n) reduction was 49.0% (120), 47.3% (104), 36.0% (6), 72.1 (10) among all elder patients, untreated, discontinued treatment and initiated treatment, accordingly; P=0.148).

A multivariable analysis indicated that a baseline UACR of > 300 mg/g Cr was associated with an OR of 1.46(95% CI 1.08-1.98) for having a reduction in UACR category compared to patients with a UACR of 30-300 mg/g. Males, patients with lower eGFR and patients with hypertension were less likely to have a reduction in UACR category (OR=0.71; 95% CI: 0.55-0.92, OR=0.57; 95% CI: 0.37-0.90and OR=0.59; 95% CI: 0.45-0.79, respectively). Patients in the lowest SES category (1-3) were more likely to have a reduction in UACR category than higher SES categories (4-5 and 6-8) (Table 3).

Discussion

In this retrospective cohort study of T2DM and albuminuria, patients initiating sitagliptin therapy added to metformin experienced a statistically significant reduction in urinary albumin excretion. The effect of DPP-4i on albumin excretion in patients with T2DM and albuminuria was evaluated in previous studies [13-16]. Two small, open-label, studies with sitagliptin demonstrated a treatment-dependent decrease in UACR in patients with T2DM [13-14]. A pooled analysis of data from four double-blind, placebo-controlled studies conducted with linagliptin investigated changes in UACR [15]. Exposure to linagliptin was associated with statistically significant reductions in UACR versus placebo. In the SAVOR trial [16], 16,492 adult patients with T2DM at high risk for cardiovascular events, who were treatment naïve or on any background of antihyperglycemic therapy (except incretins), were randomized to saxagliptin or placebo. Patients receiving saxagliptin had less development and less progression of microalbuminuria. Our results based on observational data that reflects clinical practice in Israel are in line with these publications and add additional data supporting the concept that DPP-4i as a class have potential reno-protective effects and may lead to reduced urinary albumin excretion [17]. Furthermore, the beneficial effect of Sitagliptin on albuminuria can be observed as early as 3 months [18], justifying the use of 120 days as the minimum follow-up time to capture the drug effect on UACR in our study.

Recent studies have confirmed the presence of the DPP-4 enzyme in multiple sites in the kidney including renal endothelium, renal tubles and glomeruli [19,20]. In addition, GLP-1 receptors have also been localized to the renal tubule and vasculature [21]. Experiments using a variety of animal models including GLP-1 -/- animals have shown that DPP-4 inhibition and GLP-1 agonism modulate sodium and water homeostasis improved endothelial function and inhibit fibrosis. These studies also reported both decreased proteinuria and albuminuria suggesting that inhibiting DPP-4 enzyme may improve renal function independent of change in blood glucose by a variety of

Table 1: Baseline characteristics of study population.

Total n= 1248	Category	n (%)
Sex	Male	834 (66.8)
	Female	414 (33.2)
Age (Years)	<45	64 (5.1)
	45-64	695 (55.7)
	65-74	348 (27.9)
	75+	141 (11.3)
	Mean ±SD (Median)	62.5 ± 10.0 (62.5)
Diabetes Duration (Years)	<2	63 (5.0)
	2-5	174 (13.9)
	5-10	475 (38.1)
	10+	536 (42.9)
UACR (mg/g Creatinine)	30-300	1011 (81.0)
	>300	237 (19.0)
HbA1c (%)	<7.0%	201 (16.1)
	7.0-7.4%	233 (18.7)
	7.5-7.9%	206 (16.5)
	8%+	591 (47.4)
	Unknown	17 (1.4)
	Mean ±SD (Median), n= 1231	8.2 ± 1.4 (7.9)
eGFR (mL/min/1.73 m^2)	60+	1121 (89.8)
	45-60	127 (10.2)
BMI (kg/m^2)	<30	516 (41.3)
	30-35	404 (32.4)
	35+	297 (23.8)
	Unknown	31 (2.5)
	Mean ±SD (Median), n= 1217	31.7 ± 5.4 (31.0)
Hypertension	Yes	971 (77.8)
History of CVD*	Yes	390 (31.3)

*based on ICD-9 codes for ischaemic heart disease; myocardial infarction; congestive heart failure; peripheral vascular disease; cerebrovascular disease; transient ischaemic attack; atrial fibrillation; prior coronary artery bypass grafting; or percutaneous coronary intervention.

Table 2: Percent Change in UACR according to baseline characteristics.

Parameter	Category	n	Mean	SD	Median	P-Value *
Overall UACR Change **		1,040	-9.3	94.7	-31.8	<.001
Sex	Male	685	-8.0	89.3	-27.8	0.004
	Female	355	-12.0	104.2	-38.9	
Age (Years)	<45	50	-8.9	87.0	-33.8	0.098
	45-64	581	-7.0	98.6	-28.6	
	65-74	289	-9.8	86.1	-30.0	
	75+	120	-19.6	98.4	-49.0	
Baseline HbA1c (%,mmol/mol)	≤8, 64	576	-4.2	101.9	-26.8	0.121
	>8,64	450	-15.0	85.3	-37.6	
HbA1c (%) Change	>0	222	15.3	111.8	-13.4	<.001
	0-(-0.49)%	227	0.0	96.3	-22.2	
	(-0.50)-(-1.00)%	259	-16.4	93.0	-37.0	
	< (-1.00)%	299	-25.4	80.1	-46.0	
Change in ACE inhibitors/ARB	Untreated	109	-18.3	76.5	-25.0	0.030
	Ongoing therapy	832	-6.7	95.2	-29.0	
	Discontinue therapy	25	4.6	168.4	-36.5	
	Therapy initiation	74	-30.5	75.8	-50.1	
Change in NSAIDs	Untreated	109	-18.3	76.5	-25.0	0.337
	Ongoing therapy	832	-6.7	95.2	-29.0	
	Discontinue therapy	25	4.6	168.4	-36.5	
	Therapy initiation	74	-30.5	75.8	-50.1	
Baseline UACR (mg/g Creatinine)	30-300	968	-7.9	96.9	-30.7	0.209
	>300	72	-28.4	53.9	-42.9	
BMI	≤30	447	-19.0	82.7	-37.5	0.007
	>30	567	-2.5	100.6	-27.3	

Change in UACR according to baseline characteristics. * P-values were calculated by Wilcoxon sum rank test and Kruskal-Wallis test for comparisons of two categories and more than two categories, respectively.**UACR difference is statistically significant different from zero, P-value was calculated by Wilcoxon signed Rank test.

Abbreviations: SD: Standard Deviation; UACR: Urinary Albumin/Creatinine Ratio; ACEi: Angiotensin Converting Enzyme Inhibitors; NSAIDs: Non-Steroid Anti-Inflammatory Drugs; ARB: Angiotensin Receptor Blockers; BMI: Body Mass Index

Table 3: Multivariable Logistic Regression Model for a Reduction in UACR Category among Sitagliptin Users.

Parameter	Category	n	OR	Lower 95% CL	Upper 95% CL
Sex	Female	414	1 (ref)		
	Male	834	0.708	0.546	0.918
Age (Years)	<65	759	1 (ref)		
	65+	489	1.243	0.957	1.614
Baseline UACR (mg/g Creatinine)	30-300	1011	1 (ref)		
	>300	237	1.462	1.078	1.983
Baseline HbA1c(%)	<=8%	682	1 (ref)		
	8%+	549	1.080	0.841	1.387
	Unknown	17	1.130	0.404	3.163
Level of Socioeconomic Status	1-3 (Lowest)	126	1 (ref)		
	4-5	249	0.563	0.355	0.892
	6-8	600	0.672	0.447	1.011
	9-10 (Highest)	246	0.885	0.560	1.400
	Unknown	27	0.609	0.243	1.522

Table 3: Multivariable Logistic Regression Model for a Reduction in UACR Category among Sitagliptin Users.

Parameter	Category	n	OR	Lower 95% CL	Upper 95% CL
eGFR (mL/min/1.73 m^2)	60+	1121	1 (ref)		
	45-60	127	0.574	0.367	0.897
Hypertension	No	277	1 (ref)		
	Yes	971	0.595	0.446	0.793
BMI (kg/m^2)	<=30	516	1 (ref)		
	30+	701	0.803	0.622	1.036
	Unknown	31	0.779	0.345	1.758

Abbreviations: OR: Odds Ratio; CL: Confidence Limit; UACR: Urinary Albumin/Creatinine Ratio; eGFR: Estimated Glomerular Filtration Rate; BMI: Body Mass Index

mechanisms [5,22].

In this study the magnitude of improvement in UACR was weakly associated with HbA1C reduction. Additionally, the reduction in UACR was significant in the sitagliptin treated subgroup with no reduction in HbA1c suggesting that the effect of DPP-4i may also be independent of its hypoglycemic effect. This is in line with previous studies showing the ability of DPP-4i to ameliorate albuminuria in mice with diabetes independent of their glucose lowering effects [5,19]. As in any self-controlled study, regression to the mean is a potential bias in interpreting our results [24]. To address this concern, we compared baseline UACR values with a prior measurement (225 days before index date on the average) as reported in the patient's medical record. The difference between the two median baseline measurements with UACR values higher than 30 mg/g Cr (n=935) showed that the two measurements were nearly identical (difference = 0.00). These findings markedly reduce the possibility that our observations among treated patients represent regression to the mean.

The validity and generalizability of the UACR data in MHS has been established in previous studies, including a meta-analysis of the international CKD Prognosis Consortium [25].

This large cohort study is limited by its self-controlled study design and results should be interpreted cautiously. Our observational study is however in line with earlier work that suggests DPP-4 inhibition may confer a reno-protective albumin reducing effect which is glucose independent. To examine this further a comparative analysis to patients with albuminuria treated with other hypoglycemic agents and controlled for glucose improvement is needed. Moreover, having access to long-term treatment periods will also allow analysis of DPP-4 effects on kidney function beyond albuminuria.

CONCLUSION

This observational study indicates that sitagliptin added to metformin may decrease UACR in most patients with T2DM and incipient nephropathy in clinical practice, independent of its effect on HbA1c. Whether this represents a glucose-independent DPP-4 mechanism needs further study.

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CONFLICT OF INTEREST

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Kaan Tunceli, Shengsheng Yu, Ofer Sharon, Kim Brodovicz, Noga Gadir, Harvey Katzeff, Bernd Voss, Larry Radican - Merck employees and stockholders at the time of the study. Kim Brodovicz is currently an employee of Boehringer Ingelheim; Noga Gadir is currently an employee of Pfizer.

Cheli Melzer-Cohen , Gabriel Chodick, Varda Shalev, Yasmin Maor -None declared

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