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Research Article

Impact of Point of Care Albuminuria on Therapeutic Inertia in Patients with Type 2 Diabetes and Hypertension

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Abstract

Objective: Therapeutic inertia in type 2 diabetes (T2D) is particularly evident for albuminuria that does not receive full attention from treating practitioners. Our objective was to assess whether we could help overcome therapeutic inertia of T2D hypertensive patients with a point of care measure of blood pressure and albuminuria on quality of care.

Methodology: CLINPRADIA (CLINical PRActice in DIAbetes (NCT01907958)) was a multicenter randomized trial in family practice clinics in Canada to evaluate the impact of introducing a device allowing a point-of-care testing (POCT) of urinary albumin excretion to usual practice on the management of albuminuria in T2D patients with hypertension. A total of 8 sites (4 in Quebec and 4 in Ontario) with at least 5 general practitioners each were involved in the study totaling 243 patients with uncontrolled hypertension (i.e., BP>130/80 mmHg) who were followed for a period of 12 months. The clinics that had access to the POCT of blood pressure and albuminuria at some point during the study formed the intervention group while the clinics that did not have access to the information at any time during the study were included in the control group.

Results: Baseline characteristics of control and intervention groups were not different in age, sex, blood pressure (BP), blood glucose control and kidney function. By the end of the study, the decrease in albuminuria from log ACR 0.357 to 0.017 was significant ($p<0.002$) in the intervention group only. Its lowering was more significant ($p<0.01$) with ACEi or ARBs combined with CCB than with the medications alone or with any other medications. These combinations led also to a significant reversal of eGFR decline. At the end of the study, the average SBP were 129 and 137 mmHg in the intervention and control groups, respectively (difference $p=0.004$), so that more patients had their blood pressure controlled in the intervention group.

Conclusion: Provision of timely information of blood pressure and albuminuria levels of T2D patients helped overcome therapeutic inertia.

Keywords: Type 2 Diabetes; Hypertension; Diabetic Nephropathy; Albuminuria; Therapeutic Inertia; POCT

List of Abbreviations

ACEi	:	Angiotensin Converting Enzyme Inhibitors
ACR	:	Albumin Creatinine Ratio
ADVANCE	:	Action in Diabetes and Vascular disease: Preterax and Diamicron mr Controlled Evaluation
ANOVA	:	Analysis of Variance
ARB	:	Angiotensin Receptor Blockers
BP	:	Blood Pressure
CCB	:	Calcium Channel Blockers
CHEP	:	Canadian Hypertensive Education Program
CHUM	:	Centre Hospitalier de l'Université de Montréal
CI	:	Confidence Interval
CKD	:	Chronic Renal Disease
CLINPRADIA	:	Clinical Practice in Diabetes
eGFR	:	Estimated Glomerular Filtration Rate
FHT	:	Family Health Teams
GMF	:	Group of Family Medicine
GPs	:	General Practitioners
HbA1C	:	Glycated Haemoglobin
IQR	:	InterQuartile Range
MA	:	Microalbuminuria
NS	:	Not Significant
POCT	:	Point-Of-Care Testing
PPV	:	Positive Predictive Value
SBP	:	Systolic Blood Pressure
SE	:	Standard Error
T2D	:	Type 2 Diabetes
UACR	:	Urinary Albumin Creatinine Ratio
UKPDS	:	UK Prospective Diabetes Study
VIF	:	Variance Inflation Factor

Introduction

Diabetes is a major burden on the health of populations worldwide. According to the International Diabetes Federation ATLAS, in 2021 an estimated of 537 million adults aged 20–79 years are currently living with diabetes worldwide which represents 10.5% of the world's population in this age group [1]. This number is predicted to rise to 783 million in 2045 with standardised prevalence to each national population of 12.2% [1]. People with T2D are at substantially increased risk of developing complications, both macrovascular (coronary heart disease and stroke) and microvascular (retinopathy and nephropathy).

Hypertension is present in half of patients with T2D at diagnosis, with hypertension developing later in the course of the disease in most of remaining patients. When combined with hypertension, diabetes risk of developing complications increases. The most common and potentially devastating complication of diabetes is chronic kidney disease (CKD). An approximate 40% of people with diabetes have CKD and CKD associated with diabetes is the leading cause of kidney failure in Canada [2,3]. Classic diabetic nephropathy progresses over many years from subclinical disease (microalbuminuria, MA) to overt nephropathy (with lowering of eGFR) to end-stage renal disease, to dialysis and renal transplantation presenting a significant burden in Canada with over 4 million Canadians suffering from chronic renal diseases [4].

Progression of diabetic nephropathy can be slowed down with medications that disrupt the renin-angiotensin-aldosterone system [5]. In T2D patients, Angiotensin Converting Enzyme inhibitors (ACEi) and Angiotensin Receptor Blockers (ARB) have been shown to decrease albuminuria, prevent worsening of nephropathy and reduce the risk of developing new nephropathy [6-8]. In ADVANCE trial, ACEi based therapy was able to achieve most significant primary prevention of microalbuminuria [9]. This intensive control of blood pressure to <135/85 resulted in lowering total mortality in this clinical trial [10]. Over last few years, novel classes of medication, including sodium glucose-cotransporter type 2 inhibitors, glucagon-like peptide-1 receptor agonist and selective, non-steroidal mineralocorticoid receptor antagonist, were demonstrated to decrease and prevent renal as well cardiovascular events. The combination of cardiovascular and kidney complications has become known as cardiorenal complication [11-13]. It has been shown that urinary albumin to creatinine ratio (UACR) is the most efficient modifiable traditional risk factors to predict cardiovascular mortality, heart failure, and stroke in the general population [14]. Although a good predictor of cardiovascular mortality, eGFR was not found to be as good as UACR particularity due to its initial non-linear risk impact.

The current recommendation is to measure UACR at the diagnosis of T2D and yearly thereafter, when no other causes

of albuminuria or low estimated glomerular filtration rate (eGFR) are present, and when acute renal failure or non-diabetic kidney disease is not suspected [15]. In addition, persistent microalbuminuria, defined by at least 2 of 3 tests positive taken at 1- to 8-week intervals, should be demonstrated before the diagnosis of nephropathy is made.

American Diabetes Association signals the importance of therapeutic inertia in T2D by not achieving well demonstrated targets, recommended by advisory bodies and the need to improve the status quo [16,17].

Point of care testing (POCT) HemoCue is a device allowing immediate testing found to be sufficiently accurate correlating with laboratory estimations. Preliminary evidence of the POCT benefit in diabetes outpatients already exist. Heidkamp et al. examined whether systematic screening for urine albumin using a POCT in outpatients with diabetes increased the frequency of the diagnosis of nephropathy [18]. The study was conducted in 15 primary physicians' offices in 2002 (12 months) as control versus 2003 (3 months) when HemoCue Urine Albumin® POCT was available, on a total of 2211 diabetic outpatients. In the control group, 15% of patients were diagnosed with microalbuminuria compared 41% during 3 months when using HemoCue. The authors concluded that systematic examinations of urinary albumin by the HemoCue Urine Albumin® POCT result in a higher frequency of diagnosis of nephropathy [18].

Our objective was to assess whether a point-of-care testing of albuminuria in management of hypertensive T2D patients could help overcome therapeutic inertia by providing physicians with a point of care measure of blood pressure and albuminuria [17] to improve treatment. Further objective was to evaluate the impact of POCT on the rate of diagnosis of albuminuria or CKD. Finally, overall satisfaction of health care professionals was also monitored.

Methods

Clinpradia study was a multicenter stepped wedge cluster randomized trial of family practice clinics in Quebec and Ontario comparing the effect of introducing at different times a POCT for urine albumin to usual practice on quality of care in hypertensive patients with T2D. The study was performed at 8 sites with at least 5 General Practitioners (GPs) in each clinic: 4 Groups of Médecine Familiale (GMF) in Quebec and 4 Family Health Teams (FHT) in Ontario with at least 35 patients per clinic. The objective was to recruit a total of 280 subjects over a period of 3 months. The recruitment period had to be extended to 6 months. Inclusion criteria included T2D adults (>18 years) male or female with ongoing anti-diabetic therapy for at least 5 years and uncontrolled hypertension (i.e. BP>130/80 mmHg). Patients signed informed consent form for conduct of this study that was approved by ethics committee of coordinating center and by each participating clinic. The data analysis was approved by the ethics committee of the Centre Hospitalier de l'Université de Montréal (CHUM). Patients with type 1 diabetes or who were already on therapy used in ADVANCE trial or allergic to ACEi or sulfonamide derivatives were excluded from the study. Other exclusion criteria were severely impaired renal function, angioedema related or not to previous treatment with ACEi, hyperkalemia or hypokalemia, severe hepatic impairment, use of non-antiarrhythmic agents causing torsade de pointes, pregnant or lactating women and any other conditions which may impact on participation according to treating physician.

Data were collected at entry and at each visit occurring every 3 months for a period of one year. Three clinical sites in Quebec and 3 in Ontario were randomly assigned to the intervention group. The sites in Ontario were Welland McMaster Family Health Team, Albany medical clinic and Stoney Creek. The sites in Quebec were Clinique du Centre Médical des Générations, Clinique médicale Angus, and Fleury. One site in Ontario (Kingston Family Health Team clinic) and one in Quebec (Clinique médicale Maisonneuve-Rosemont) were assigned to the control group.

In the sites allocated to POCT, patients underwent a measure of their urinary albumin excretion using POCT, on the morning urine or urine spot, just before their appointment with their treating physician accompanied by their blood pressure results as well as CHEP guidelines of recommended BP and albuminuria targets. A urine sample was also collected at baseline and at each visit (5 collections). These urine samples were frozen and were sent to a central laboratory for the determination of ACR at the end of the study for the estimation of the correlations between urine albumin measured by POCT and laboratory determined UACR.

Before the study, participating physicians attended an investigator meeting during which CHEP guidelines for the management of hypertension in diabetic patients were refreshed and study objectives [19], design and procedures were explained. The results of the ADVANCE trial were also discussed during that meeting [20].

A total of 249 subjects were enrolled in the clinical study. Of those, 4 patients were excluded from analysis because one site closed just after the start of the study and 2 were excluded because they did not meet the inclusion criteria. Patient attrition during the study was as follow: 10 patients withdrew and one deceased after baseline visit. 6 patients withdrew, 2 missed their visit and one patient deceased after the second visit. 4 patients withdrew after the third visit and 3 patients missed their visit. Finally, 8 patients missed their final visit or withdrew from the study after the fourth visit. 213 patients were followed until the end of the study.

Statistical Analyses

Results are presented as mean and SE for continuous variables with normal distribution and as numbers and percentage for categorical variables. Baseline characteristics p values were calculated using chi-squared test or one-way analysis of variance, as appropriate. Difference in number of patients with albuminuria or with hypertension p values were evaluated using the Fisher's exact test or McNemar's test, as appropriate. P values of the mean difference between treatments were calculated using paired t-test and by Wilcoxon paired test for median differences between interventions. Logarithms of ACR values were analyzed because ACR value did not follow a normal distribution. All p values were statistically adjusted using the variance inflation factor (VIF). The VIF was calculated from the intraclass correlation coefficient. A value of $p<0.05$ was considered statistically significant. Analyses were made using R statistical software version 1.2.1335 (R core team, 2019) [21].

Results

Performance of the POCT HemoCue device in detecting albuminuria

The measures between the POCT albumin values and laboratory ACR results were correlated confirming the validity of using this point of care device (Table 1). The mean Pearson correlation coefficient calculated at each visit between the ACR (mg/mmol) and the POCT urine albumin values (mg/L) was 0.47 and was statistically significant at each visit (Table 1). As the POCT could not differentiate between micro and macro albuminuria, the two were combined and compared to normoalbuminuria for the laboratory ACR values. Taking the laboratory ACR value as the standard, the POCT test exhibited an average positive predictive value of 62% and a negative predictive value of 90% along the visits. The sensitivity and specificity of the POCT in detecting albuminuria were 88% and 67%, respectively over one-year period.

	Baseline (n=56)	3 months (n=78)	6 months (n=128)	9 months (n=120)	12 months (n=115)	Average
Positive predictive value (%)	74	64	64	54	54	62
Negative predictive value (%)	86	89	86	92	95	90
Sensitivity	88	87	84	89	92	88
Specificity	70	67	69	61	65	67
Pearson correlation coefficient r^2	0.55	0.44	0.25	0.48	0.61	0.47
P value	2.0e-05	5.6e-05	0.0047	1.7e-07	5.6e-13	

Table 1: Performance of the POCT to predict albuminuria status

Effect of the introduction of blood pressure and albuminuria at the clinical sites

The baseline characteristics of participants are depicted in Table 2. The mean age of 66.5 years was not different between the intervention and control groups (P trend=0.663). There were more men than women in both groups. At baseline, 91% of patients had a blood pressure over 130/80 mmHg with an average systolic blood pressure of 144 mmHg and an average diastolic blood pressure of 78 mmHg in the total sample (Table 2). At entry, 36% of participants had albuminuria and 74% had an HbA1c>6.5%. 84% of hypertensive T2D patients in the study were already treated for hypertension with 1.75 medication classes on average. These results highlight therapeutic inertia when the therapeutic targets are not met.

Clinical characteristics	Control group (n=81)	Intervention group (n=162)	Total (n=243)	p-value for trend*
Age (years)	67.5±1.1	66.5±0.9	66.5±0.7	0.663
Sex (% men)	51 (63.0)	105 (64.8)	156 (64.2)	0.899
Blood pressure				
Systolic blood pressure (mmHg)	145±2	144±1	144±1	0.691
Diastolic blood pressure (mmHg)	76±1	79±1	78±1	0.373

Blood glucose control				
HbA1c (%)	7.4±0.1	7.3±0.1	7.4±0.1	0.876
Fasting blood glucose (mmol/L)	8.2±0.3	7.9±0.2	8.0±0.2	0.571
Kidney function				
Plasma creatinine (µmol/L)	88.4±4.6	88.4±2.0	88.4±2.8	0.989
eGFR (mL/min/1.73m^2)	76.9±2.4	75.9±1.7	76.3±1.4	0.831
UACR logarithm mean	0.27±0.08	0.36±0.05	0.34±0.05	0.661
UACR (mg/mmol) (median IQR)	1.27(3.55)	1.79(6.64)	1.45(5.38)	
eGFR: estimated glomerular filtration rate; HbA1c, glycated hemoglobin; IQR, interquartile range; UACR, urinary albumin creatinine ratio. Note: Data are presented as mean ± SE or n (%). *Based on chi-squared test or ANOVA, as appropriate.				

Table 2: Baseline demographic and clinical characteristics.

The decrease in log ACR from 0.357 to 0.017, between first and last visit, was highly significant (p=0.0002) in the intervention group while it was not significant (p=0.227) in the control group (Figure 1). By the end of the study, the percentage of patients with albuminuria decreased significantly (p=0.030) by 26% in the intervention group while it increased by 30% (p=0.092) in the control group (Table 3).

Visits	**Control group**	**Intervention group**	**p-value***
	Albuminuria		
n	56	118	
Baseline n, (%)	16 (29)	51 (43)	0.069
12 months n, (%)	23 (41)	38 (32)	0.308
p-value*	0.092	0.030	
	Hypertension		
n	67	141	
Baseline n, (%)	62 (93)	125 (89)	0.531
12 months n, (%)	42 (63)	70 (50)	0.223
p-value*	4.01e-04	7.56e-11	
*Based on Fisher's exact test or McNemar's test, as appropriate.			

Table 3: Albuminuria and hypertension patient status changes between baseline and last visit.

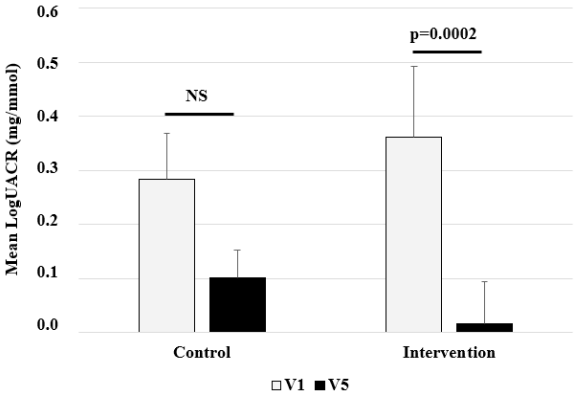

Figure 1: Mean of Logarithm of urinary albumin creatinine ratio (LogUACR) at visit 1 (V1, baseline) and visit 5 (V5, 12 months) for control and intervention groups. NS, not significant.

At the beginning of the study, the average SBP was similar between the two groups (Figure 2). Over the course of the study, the decrease in SBP was more important in the intervention group, so that at the end, the average SBP was 129 mmHg in the intervention and 137 mmHg in the control groups, with a significant difference between the two (p=0.004). Hence, the decrease in the number of patients with uncontrolled hypertension was highly significant in both groups but the percentage of participants with uncontrolled hypertension at the end of the study was lower in the intervention group (50%) than the control group (63%) group (Table 3).

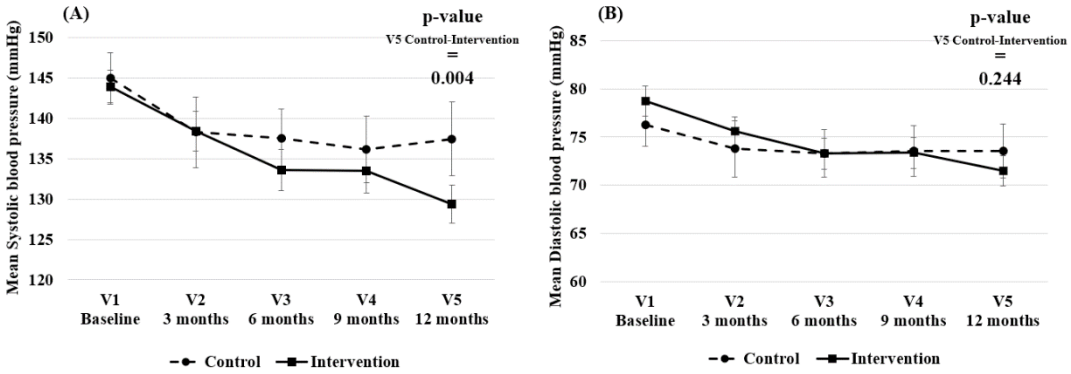

Figure 2: Mean systolic (A) and diastolic (B) blood pressures at each visit for both compared control and intervention groups. p-value based on ANOVA test. V, visit.

Effects of prescribed medication on BP, albuminuria and eGFR

The mean systolic blood pressure decreased significantly in all participants who received an ACEi or an ARB alone or in combination with a CCB (Figure 3A). The decrease in ACR was only significant with the combination of an ACEi or an ARB with CCB ($p<0.01$, Figure 3B). The decline of eGFR in patients who were taking an ACEi or an ARB was overcome by their combination with a CCB (Figure 3C).

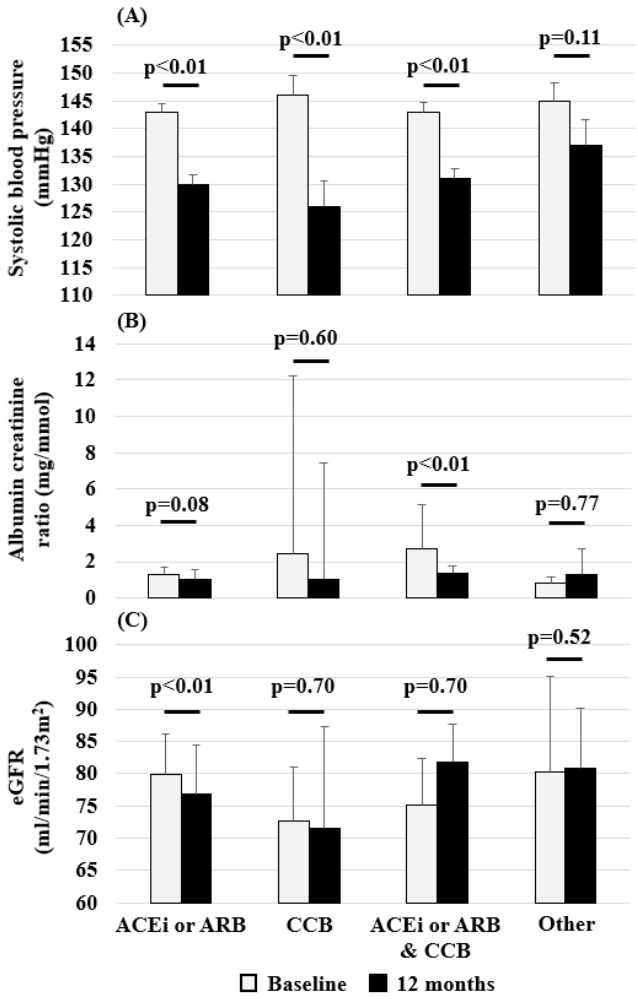

Figure 3: Effect of medication on (A) systolic blood pressure (n=190), (B) albumin creatine ratio (n=176) and (C) eGFR (n= 213) between baseline and the 12 months visit. Data are in (A) mean ± SE and p-value based on paired t-test and (B-C) median ± 95%CI and p-value based on Wilcoxon paired test. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; CCB, Calcium channel blockers; CI, Confidence interval; eGFR, estimated glomerular filtration rate.

Discussion

The POCT is a good indicator of the albuminuria, however with a positive predictive value, PPV of 62%, the positive results from the HemoCue device should be confirmed by a laboratory test of UACR [22]. This is in part attributable to the fact that contrary to a laboratory value of UACR, the values obtained with the POCT are not corrected for the amount of creatinine in the urine sample. The POCT has a high sensitivity of 88% and therefore a good ability to correctly identify patients with albuminuria. The negative predictive value is high (90%) meaning true negatives. However, its specificity is only 67% which means that some normoalbuminuric people may receive a false positive result with the POCT.

In this study, we showed that the timely information of patient's blood pressure and albuminuria can help improve albuminuria and blood pressure control in T2D patients with hypertension. Introducing the POCT at the clinic allowed for a relative risk reduction of 22% in albuminuria in the intervention group compared to the control group. This relative risk reduction is of the same magnitude (21%, p=0.003) of the one observed by intensive blood pressure control during a period of 4.5 years and twice as high as the one observed in the intensive glucose treatment group of the ADVANCE trial [10,23]. Having access to the albuminuria value at the clinic at each visit allows for a better follow-up and thereby a rapid reduction of its values within a year. This information promotes early screening and treatment modification, i.e decreasing therapeutic inertia.

All participating physicians had access to blood pressure values and CHEP guidelines initial instruction which resulted in an initial decrease of SBP in both groups (Figure 2). This initial drop in SBP reflected the positive impact usually observed in patients who take part in a clinical study [24]. At the end of the study, the intervention group reached a mean systolic blood pressure of 129 mmHg which is within the recommended value of the CHEP [25]. The average systolic blood pressure in the intervention group decreased by 14 mmHg in one year. According to the UKPDS a decrease of 10 mmHg results in a reduce risk of macro and microvascular complications [26].

While ACEi or ARB or CCB were each effective in lowering of blood pressure, only their combination was also effective in preventing the decline of eGFR confirming the nephroprotective effect of such combination [27].

Finally, the Physician's satisfactory survey showed that the physicians had a positive view on their participation in the study. Most of them thought that the POCT was useful in improvement of management of their T2D hypertensive patients.

Conclusion

There is a clear need for improvement in diagnosis and management of albuminuria in T2D hypertensive patients. The implementation of a POCT for albuminuria and blood pressure increased the number of patients at target SBP and normal albuminuria. High blood pressure and HbA1c are imperfect indicators of kidney damage that needs to be directly assessed by the measure of urinary albumin at point of care, i.e. at each visit.

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Author Contribution Statement

All authors discussed the results and commented on the manuscript. PH and JT conceived the study, supervised the findings and corrected the manuscript. JK developed the design of the study and corrected the manuscript. LS performed the analytical calculations and wrote the first draft of the manuscript. MH helped with the analytical analysis and drafted the figures and tables. RT performed the statistical analyses. M-R G collected the clinical data and supervised the clinical sites. PD helped with the technical details of the clinical study.

Author Disclosures

JT and PH received grants from Servier Canada and are shareholders of Medpharmgene. The other authors have no conflicts of interest to declare.

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