Therapeutic Inertia in the Management of Proteinuria Among Type 2 Diabetes Patients in Hong Kong Primary Care Setting: Prevalence and Associated Risk Factors

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Abstract

Background: Proteinuria is a well-known predictor of poor renal and cardiovascular outcomes in T2DM patients

Methods:

Objectives: To explore the prevalence of Therapeutic inertia (TI) on proteinuria management among T2DM patients in primary care and possible patients' and doctors' factors.

Study design: Cross-sectional study

Subjects: T2DM patients with microalbuminuria and macroalbuminuria from 1/1/2014 to 31/12/2015.

Outcome assessments: The prevalence of TI on proteinuria management and its association patients' factors and the working profile of the attending doctors.

Results: 5, 163 (26.4%) patients had diabetic nephropathy (DMN) with micro- or macroalbuminuria. Among the sampled 385 patients with DMN, TI was found to be 40.3%. Doctor factors for higher TI rate include male sex and doctors with longer duration of clinical practice and who have never received any form of Family Medicine training. Patients factors include lower average systolic (SBP) and diastolic blood pressure reading. Patients' SBP reading and microalbuminuria were negative association factor whereas doctor's year of clinical practice being over 21 years and patients being treated with submaximal dose of medication were positive association factors to TI.

Conclusions: TI is commonly present on proteinuria management among T2DM patients managed in the primary care. Patient's systolic blood pressure reading, microalbuminuria level, Dr's year of clinical practice and dose of ACEI/ARB were found to be associated with the presence of TI. Further study on the barriers and strategies to combat TI is needed to improve the clinical outcome among T2DM patients.

Background

Type 2 diabetes mellitus (T2DM) is one of the most common chronic conditions encountered in primary care and affects up to 10% of the Hong Kong population (1). Proteinuria, including microalbuminuria and macroalbuminuria, is well-known predictor of poor renal outcomes in T2DM patients and more recently, to be a predictor of cardiovascular outcomes in these populations (2, 3). There is emerging data that reduction of albuminuria leads to reduced risk of adverse renal and cardiovascular events (4,5).

Effective treatments for preventing development and progression for diabetic kidney diseases are available. Angiotensin-converting enzyme inhibitors (ACEI) reduced the risk of new-onset of microalbuminuria, macroalbuminuria or both and death when compared to placebo for T2DM patient with or without hypertension (6,7). Although similar effects were not observed in Angiotensin II receptor blockers (ARB), meta-regression suggested possible benefits from ARB for preventing kidney disease in

high risk patients (8,9). Based on these evidences, the American Diabetes Association (ADA) guidelines currently state that all patients with diabetes mellitus and micro- or macroalbuminuria should be prescribed an ACEI or ARB to mitigate nephropathy (10).

Despite all these evidences, proteinuria control among diabetic patients has been inadequate in the primary care settings both internationally and locally. Studies from the United States have shown that the overall prevalence of micro-, and macroalbuminuria was 39% and 10% respectively among T2DM patients (11). However, among T2DM patients diagnosed with nephropathy, only 25% were receiving ACEI/ARB as per ADA guidelines has suggested (12). Similar studies carried out at local primary care settings have reported that the prevalence of microalbuminuria among T2DM patients was 13.4% and the condition was significantly associated with advanced age, female sex, poor glycaemic control, and coexisting hypertension (13). In addition, as shown by another study looking at the complications among Chinese T2DM patients in urban primary care clinics, only about half of diabetic patients with micro- or macroalbuminuria were treated with ACEI, or ARB (14).

Like other chronic conditions, reasons for poor proteinuria control are multifactorial and may include patient-, physician- and care delivery factors. Among them, suboptimal medication augmentation has been identified as an important physician factor. This is known as therapeutic inertia (TI). It is defined as whenever the health-care provider does not initiate or intensify therapy appropriately when therapeutic goals are not reached: “recognition of the problem, but failure to act” (15–16). TI has become increasingly acknowledged as a major impediment for CVD risk factor control. Indeed, in another study carried out by the author’s research team, TI has been present in lipid management in over 60% of diabetes patients with dyslipidemia (17).

Locally, significant proportions of T2DM patients are managed in primary care and followed up at government General Out-patient Clinics (GOPCs) of the Hospital Authority. Up to now, there was no study exploring the prevalence of TI in proteinuria management among diabetes patients managed in the primary care setting both internationally and locally. To fill this knowledge gap, our study tried to explore the prevalence of TI in proteinuria management among T2DM patients and to explore possible associating factors. By overcoming these barriers, it was expected that the progression of renal complications and the cardiovascular outcome of T2DM patients could be improved in the long run.

Aim of the study:

1. To explore the prevalence of therapeutic inertia (TI) on proteinuria management among T2DM patients managed in the primary care.
2. To explore possible associating factors in both patients’ and doctors’ perspective.

Methods

Study design: Cross-sectional study

Subjects:

Inclusion criteria:

All T2DM patients having the International Classification of Primary Care (ICPC) code T90 (Non-insulin Dependent Diabetes Mellitus), who had been regularly followed up in all GOPCs of KCC from 1 Jan 2014 to 31 Dec 2015, and had regular blood and urine checked at least once during this period were identified from the Clinical Data Analysis and Reporting System (CDARS). In our clinics, T2DM patients were usually provided with blood and urine check-ups at least annually to every 18 months. This 2-year retrieval period was therefore likely to cover all such patients regularly followed up in our cluster. The diagnosis of diabetes was based on the "Definition and description of diabetes mellitus" from American Diabetes Association in 2013 (10).

Exclusion criteria:

1. Type 1 diabetes patients
2. Diabetes patients who had no regular blood or urine check-up during the study period,
3. Diabetes patients followed up in Specialist Outpatient Clinic

Definition of proteinuria (microalbuminuria, macroalbuminuria and high risk proteinuria) among T2DM patients

According to American Diabetes Association (ADA) guideline 2015, all T2DM patients should have urine albumin/creatinine ratio (ACR) check to screening for microalbuminuria (10).

Microalbuminuria was defined as albumin secretion of 30 to 300 mg/24 h and macroalbuminuria or overt proteinuria as a value of >300 mg/24 h. Screening for microalbuminuria can be performed by measurement of urine ACR in a random spot collection (10). Normo-albuminuria was defined as a urine ACR of <2.5 mg/mmol in males and <3.5 mg/mmol in females. Corresponding values for microalbuminuria were defined as 2.5 to 30 mg/mmol for males and 3.5 to 30 mg/mmol for females, and for macroalbuminuria they were >30 mg/mmol for both genders (18). An elevated urine ACR needed to be confirmed in the absence of urinary tract infection with additional first-void specimens collected during the next 3 to 6 months.

Definition of therapeutic inertia in management of proteinuria among T2DM patients:

In this study, management of microalbuminuria or macroalbuminuria is defined as inadequate and escalation treatment is indicated if latest urine ACR level is ≥ 2.5mmol/L in male patients and ≥ 3.5 mmol/L in female patients. Consultation notes of the follow up immediately after the latest urine ACR test being available were reviewed through the computer management system (CMS). TI is considered to be present when attending doctors failed to initiate or intensify ACEI/ARB treatment. On the other hand, if there are valid reasons documented in the medical notes justifying that escalating treatment is not feasible despite clinical indications, it will not be counted as TI.

Common justifications included:

1. ACEI/ARB is contraindicated due to drug allergy, with history of renal artery stenosis, or patients' blood pressure on attendance has been low (<90/60mmhg);
2. Patients' intolerance to the side effects of ACEI/ARB: such as with prior history of drug induced renal impairment or hyperkalemia (serum K>5.0) etc. As patients who could not tolerate ACEI due to persistent cough could be treated by ARB, failing to transfer the treatment regime will also be counted as TI.
3. Other causes of increased ACR need to be excluded, e.g. urinary tract infection etc.
4. Patients' non-compliance to the existing ACEI/ARB regime and advice on regular drug compliance was given;
5. Patients' refusal to start ACEI/ARB.
6. Patients are taking the maximum dosage of ACEI/ARB

Sample size calculation and random sampling

According to the data drawn from Clinical Data Analysis and Reporting System (CDARS) of HA, totally there were 22,644 DM patients having regular FU in GOPCs of KCC. Among them, 19,583 patients had blood and urine ACR checked at least once during the study period. Based on our definitions mentioned above, 5,163 of them had diabetic nephropathy with micro- or macroalbuminuria. Using the internet sample size calculator (Survey Software from Creative Research System, http://www.surveysystem.com), a sample size of 385 would provide 95% confidence level and 5% confidence interval. Therefore totally 400 cases were sampled to ensure adequate statistical power and allow room for case exclusion.

A list of random numbers was then generated from the research randomizer (http://www.randomizer.org/form.htm), from which the 400 patients to be included were selected. Details of the visit with latest urine ACR result seen were recorded. Data were collected by reviewing the consultation notes in CMS record of selected patients using a standard data collection form (please refer to **Appendix**) by the principle investigator and counter checked by another experienced doctor in the research team.

Determination of variables

The recruited patients' age, gender, smoking status, body mass index (BMI), latest blood pressure, hemoglobin A1c (HbA1c), serum creatinine levels, lipid profile and urine ACR were retrieved from the CMS. The most recent blood or urine test was used for analysis if more than one test had been performed during the study period. The BMI was calculated as body weight/body height^2 (kg/m^2). The patient was considered a smoker if he/she currently smoked or was in the first 6 months of stopping. Abbreviated Modification of Diet in Renal Disease (MDRD) formula was used to calculate the estimated Glomerular Filtration Rate (eGFR).

The working profile of the attending doctors was retrieved from data from Central Office of Department of Family Medicine (FM) and GOPC, KCC. Duration of clinical practice was calculated as the number of years from registration in the Medical Council of Hong Kong.

FM training status of doctors was documented and categorized according to the following criteria.

Group 1: Doctors were those who had never received any formal FM training before. Group 2: Doctors were those who had undergone basic vocational training from Hong Kong College of Family Physicians (HKCFP) or had studied the diploma of FM (DFM).

Group 3: Doctors were intermediate fellow who had obtained the fellowship in HKCFP.

Group 4: Doctors were FM specialists who have obtained the fellowship in Hong Kong Academy of Medicine HKAM (FM).

Statistical Analysis

All data would be entered and analyzed using computer software (Windows version 21.0; SPSS Inc, Chicago [IL], US). Student's t test and analysis of variance were used for analyzing continuous variables and the Chi square test for categorical data. Fisher Exact test was used if the sample size was less than 5. Multivariate stepwise logistic regression would be done to determine the association between TI and the significant different variables from patients' characteristics and doctors' characteristics. All statistical tests were two sided, and a P value of less than 0.05 was considered statistically significant.

Ethical Consideration

The Ethical Approval was granted by the Research Ethical Committee (Kowloon Central/Kowloon East Cluster) on 5/8/2016 (Ref: KC/KE-16-0109/ER-1)

Results

A total of 22,644 T2DM patients were identified from KCC GOPC Diabetes Mellitus registry from 1 Jan 2014 to 31 Dec 2015. Among them, 19,583 (86.5%) patients had their blood and urine ACR checked at least once during the above period; 5163 (26.4%) patients were found to have diabetic nephropathy (DMN) with microalbuminuria (n=4132, prevalence rate 21.1%) or macroalbuminuria (n= 1031, prevalence rate 5.3%).

Among the 400 randomly sampled diabetic nephropathy patients, 15 cases were excluded including 14 cases being FU regularly by Specialist SOPD and 1 case with wrong diagnosis. The remaining 385 patients were included for data analysis **(Figure 1)**.

Table 1 summarized the demographic characteristics of the recruited patients. The mean age of the study population was 70.0 ± 12.6 years and 195 patients (50.6%) were female. The mean duration of diabetes was 9.8 ± 8.1 years. Regarding to their co-morbidities, 360 (93.5%) patients had concomitant HT, 20

(5.2%) had IHD, 43 (11.2%) had CVA, and 1 (0.3%) had PVD. Mean urine ACR level was 35.9 ± 84.0 mg/mmol). 75.8% of the cases (n=292) were found to have microalbuminuria and 24.2% (n=93) were found to have macroalbuminuria. Among the 385 cases, only half of the cases were treated with ACEI (n=194) and 16.1% were treated with ARB (n=62).

Table 2 summarizes the demographic profiles of physicians who have attended the recruited DM cases with proteinuria. A total of 58 doctors, among whom 23 (39.7%) were female, attended the 385 T2DM patients. The mean duration of clinical practice was 15.4 ± 9.2 years. Regarding to FM training status, 13 (22.4%) doctors had received no FM training, 13 (22.4%) received basic training or studied DFM, 16 (27.6%) were intermediate FM fellows, and 16 (27.6%) were FM specialists. Sub-analysis of attending doctors' profile according to their duration of clinical practice and FM training status is shown in **Table 2.1**. Training status of FM varied significantly with duration of clinical practice (P<0.001). Among 7 doctors who had worked for ≤5 years, all had been receiving basic FM training or had become intermediate fellow. On the other hand, among 15 doctors who had worked for over 20 years, most (n=12, 80%) had not received any formal FM training.

Table 3 shows the characteristics of physicians in TI-positive and TI-negative patients. Among 385 T2DM with micro- or macroalbuminuria, TI was identified in 155 cases, with a prevalence rate of **40.3%.** Male doctors were found to have a higher TI rate (45.3%) compared with female doctors (32.7%, P=0.014). The duration of clinical practice of attending doctors was significantly longer in the TI group (15.6± 9.4 yrs) compared with the non-TI group (11.8±7.3yrs, P<0.001), with doctors working for over 21 years having a particularly higher rate of TI (58.8%).

With regards to training status, doctors without any form of Family Medicine training were found to have a much higher rate of TI (53.8%, p=0.006). However, among the subgroups of doctors with different level of training, i.e. basic trainee, intermediate fellow or FM specialist, no significant difference was identified (p=0.525).

Table 4 summarizes the characteristics of T2DM patients in TI-positive and TI-negative groups. Patients from both groups were comparable in male to female ration, age, BMI, duration of DM, Hemoglobin A1c level, eGFR level and urine ACR level. In addition, their complication rate with stroke, IHD, PVD and diabetic complications including diabetic retinopathy and diabetic neuropathy were also similar (all P>0.05). However, most of TI-positive DM patients (85.2%) were in the micro-albuminuria range versus 69.6% in TI-negative group (P=0.001). The average systolic and diastolic BP was also found to be lower in TI-positive group than TI-negative group (P=0.000 and P=0.036).

Based on the results from **Tables 3 and 4**, multivariate stepwise logistic regression analysis was performed to identify any factors that contributed to TI (**Table 5**). Only variables that were significantly different in the univariate analysis were included in the regression model. As the FM training status varied significantly with the duration of clinical practice and these two factors were interrelated (Table 2.1, P<0.001), only one of these two variables was included in the logistic regression analysis. As the P value of years of clinical practice (P<0.000) was smaller than that for FM training status (P=0.006) in the

univariate analysis (**Table 3**), only doctors' year of clinical practice was entered into the logistic regression analysis. Logistic regression study revealed that the systolic blood pressure reading and microalbuminuria range of proteinuria were negatively associated with the presence of TI, whereas doctors' year of clinical practice being over 21 years and patients being treated with submaximal dose of ACEI/ARB were positively associated with the presence of TI.

Discussion

This was the first clinical analysis of TI in proteinuria management among T2DM patients managed locally in the primary care setting. It has provided important background information about the prevalence of TI in this group of patients. It also explored possible underlying factors from both the doctor's and patient's perspective.

Microalbuminuria is the earliest sign of diabetic nephropathy and predicts increased cardiovascular mortality and morbidity and end stage renal failure. Our study revealed that the prevalence of microalbuminuria and macroalbuminuria among T2DM patients from primary care was 21.1% and 5.3% respectively. These figures are higher than those reported from similar studies done in a primary civil servant clinic in Hong Kong which showed that the prevalence of microalbuminuria was 13.4% among T2DM patients (13). It is noted that the average age of patients in their study was 58 yrs old, which is much younger than the average age of T2DM patients recruited in this study (70.0 yrs). Since advanced age is an independent risk for the development of microalbuminuria, a higher prevalence rate of microalbuminuria in our study is expected. In addition, multiple studies conducted overseas have demonstrated that the prevalence of microalbuminuria varies among races, even within the same community (19). For example, cross-sectional studies have reported marked variation in the prevalence of microalbuminuria, ranging from 14.2% in Singapore (20), around 30% in the United States (11) and over 40% in China (21). These variations in prevalence can be attributed to factors such as differences in populations, in the definitions of microalbuminuria, method of urine collection, etc. However, this could also reflect true differences in the ethnic susceptibility to nephropathy.

Among T2DM patients included in the data analysis, 360 cases (93.5%) were found to have concomitant HT, whereas only **66.5%** of them were treated with ACEI or ARB. Based on our set criteria, therapeutic inertia was found present in **40.3%** cases, meaning that in over 40% of diabetic patients with proteinuria, appropriate drug treatment including drug initiation or dose augmentation were not provided. As there were no similar studies carried out internationally or locally, direct comparisons with other studies are not possible. However, this TI rate was much higher than the TI in glycaemic control (29–33%) among T2DM patients (22, 23), although lower than the TI rate in blood pressure (63.3–68%) (24) and lipid control (66–80%) (17) carried out by various research teams. This relatively high TI rate should alert primary care physicians the importance of proteinuria control among T2DM patients as greater TI leads to poorer clinical outcomes. Another local study from urban primary care clinics also revealed that only about half of diabetic patients with micro- or macroalbuminuria were treated with ACEI, or ARB (24). This low

ACEI/ARB prescription rate and their inadequate dose may together contribute to the suboptimal proteinuria control among T2DM patients in primary care.

Further studies of the physician profile relative to the presence of TI have revealed that male doctors, doctors with longer duration of clinical practice, particularly those with over 20 years' clinical practice, and doctors without Family Medicine training were found to have higher rate of TI. In our study, most doctors who had worked for over 20 years had no formal FM training (12 [80%] out of 15 doctors, Table 2.1). In addition, when training status was compared, doctors with no FM training had a higher rate of TI than those who have been undergoing or had finished FM training (53.8% vs 36.8%; P = 0.006). We postulate that doctors who have worked for over 20 years may be less familiar with the latest guidelines on proteinuria management, possibly due to a lack of FM or related training. If physicians lack appropriate training, there will be gaps in their knowledge of latest clinical management guidelines. Indeed, some evidence suggests that Physicians who have been in practice for more years may be less likely to deliver high-quality care or comply with treatment guideline (25, 26). Medical advances occur frequently, and the explicit knowledge that physicians possess may easily become out of date. Therefore, although it is generally assumed that the knowledge and skills accumulated by physicians during years of practice lead to superior clinical abilities; it is plausible that physicians with more experience may paradoxically be less likely to provide technically appropriate care. This has been confirmed by a systematic review performed on the relationship between clinical experience and quality of health care. It showed that, among 62 published studies that measured physician knowledge or quality of care and described time since medical school graduation or age, more than half suggested that physician performance declined over time for all outcomes measured (27). Therefore, these findings raise concerns about the adequacy of continuing professional education in medicine and alert us the need to provide quality improvement interventions to this subgroup of doctors, particularly in the primary care setting.

With regards to patient's profile, we found that TI was more prominent in patients with microalbuminuria group (85.2% of all TI patients). This could be explained by the threshold effect which is, the closer the urine ACR level is to target level, the less likely and the doctor to intensify the treatment. This threshold effect has been commonly observed in other similar studies. Other factors that contribute to the threshold effect could be "overestimation of current care" or "complacency with borderline values", leading to the physician's subjective misperception that the care provided is sufficient.

Indeed, this threshold effect was also found to be related to the inertia of treating hyperglycemia and hyperlipidaemia in T2DM patients (22, 17).

Our study also revealed that TI positive T2DM patient had a much lower average systolic and diastolic blood pressure reading compared with TI negative group. In TI positive group, a lower proportion of T2DM cases have concomitant HT (90.3% versus 95.7%, P = 0.037). In addition, 65.8% of TI positive group has satisfactory blood pressure control (< 130/80mmhg) at the clinical visit compared with TI negative group (47.8%, P = 0.0005). These data revealed that doctors are less likely to initiate or intensify ACEI or ARB treatment in normotensive albuminuria cases despite the evidence that ACEIs and ARBs reduce the risk of

progression to macroalbuminuria in normotensive T2DM patients with microalbuminuria. The possible reasons might be the concerns about the development of hypotension if ACEI/ARB is initiated or the dose is augmented. The side effects of ACEI or ARB, such as hyperkalemia and persistent throat discomfort and dry cough, are other common concerns. Although these concerns sound reasonable, lots of studies have proven that albuminuria control may slow the progression of CKD and improve the clinical outcomes among T2DM patients even in the absence of hypertension (28). In addition, normalization of microalbuminuria is associated with a reduction in the rate of decline in glomerular filtration rate. In line with these findings, international guidelines recommended that ACEIs or ARBs should be initiated in T2DM cases with microalbuminuria unless contraindicated to slow progression of diabetic nephropathy (29). Therefore, clinicians should be more proactive in initiating proteinuria control treatment to prevent the disease progression and improve the cardiac vascular outcome in the long run. At the same time, we should also strike a balance between the benefit of proteinuria control and the risk of possible hypotension and closely monitor the blood pressure level during follow up consultations.

Multiple variable logistic regression analysis revealed that systolic blood pressure reading and microalbuminuria range of proteinuria were negatively associated with the presence of TI, whereas doctor's year of clinical practice being over 20 years and patients being treated with submaximal dose of ACEI/ARB were positively associated with the presence of TI.

Strength And Limitations Of This Study

This is the first clinical analysis of TI in proteinuria management among diabetic patients managed locally in the primary care setting. It has provided important background information about the prevalence of TI in proteinuria management among diabetic patients and explored the possible underlying factors from both the doctor's and patient's perspective. These findings will help improve strategies to overcome TI in proteinuria control for these patients.

There are some limitations in this study. First, the study was carried out in one single cluster of HA and therefore selection bias might exist. These results from the public primary health care sector might not be applicable to the private sector or secondary care. Nevertheless, the present results may lay the groundwork for similar studies in the future, both locally and internationally. Second, patients with diabetes who had not had any blood testing performed during the study period were excluded (n = 3061, 13.5% of all diabetic cases). The urine ACR status of this group of diabetic patients remained unknown. This might bias the accurate measurement of TI among our target population. Third, this study relied heavily on review of consultation notes to identify justification for submaximal therapy and to determine the presence of TI. Insufficient justification for a certain treatment may have resulted in an overestimation of the prevalence of TI.

Implications To Primary Care

Our study found that TI was common in proteinuria management among diabetic patients managed in the primary care, with a prevalence of **40.3%**. Doctors with a longer duration of clinical practice and who had not received formal FM training had a higher rate of TI. Patients' systolic BP reading and microalbuminuria range of urine ACR were negatively associated with the presence of TI. Considering that a large volume of T2DM patients are managed in the primary care setting and the importance of proteinuria control to prevent the progression to CKD, comprehensive strategies with a more proactive approach should be devised to combat TI so that the cardiovascular outcome of diabetic patients can be improved. Structured continuous medical education and professional training to primary care doctors on chronic disease management should be intensified to mitigate TI. Future interventional studies are needed to evaluate the effectiveness of different improvement strategies, both on patients' and doctors' perspective, to combat TI on chronic disease management.

Conclusion

TI is commonly seen in the management of proteinuria among T2DM, with a prevalence of 40.3% in the primary care. Systolic BP and microalbuminuria range of urine ACR were negatively associated with the presence of TI, whereas submaximal ACEI/ARB dose and doctors' practicing over 21 years were positively associated with the presence of TI. Comprehensive strategies should be devised to overcome TI so that the progression to CKD could be slowed down and the cardiovascular outcome of diabetic patients can be improved.

Figure/table Legends

ACEI	angiotensin converting enzyme inhibitor
ACR	Albumin over creatinine ratio
ARB	angiotensin receptor blocker
BMI	Body mass index
BP	blood pressure
CVA	cerebrovascular accident
CVD	cardiovascular disease
DFM	Diploma in Family Medicine
DM	Diabetes Mellitus
eGFR	estimated glomerular filtration rate
FM	Family Medicine
FU	follow up
GOPC	General Outpatient Clinics
HDL	high density lipoprotein
HKAM	Hong Kong Academy of Medicine
HT	hypertension
IHD	Ischaemic heart disease
KCC	Kowloon Central Cluster
LDL	low density lipoprotein
PVD	Peripheral vascular disease
SOPD	Specialist Outpatient Clinics
T2DM	Type 2 Diabetes Mellitus
TC	total cholesterol
TG	triglyceride

Declarations

Ethics approval and consent to participate

The Ethical Approval was granted by the Research Ethical Committee (Kowloon Central/Kowloon East Cluster, Hong Kong Hospital Authority) on 5/8/2016 (Ref: KC/KE-16-0109/ER-1)

As only anonymous data were analysed and there was no patient involvement in the study, no written or verbal was obtained.

Consent for publication

The manuscript contains no individual person's data in any form

Competing interests

All authors have disclosed no conflicts of interest.

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Authors' contributions

Dr FLC, corresponding author, principle investigator

Dr CC

Dr YCL

All authors have read and approved the manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request

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Tables

Table 1. Demographic characteristics of diabetic patients who fulfilled the inclusion criteria and were included in the study.

Patient characteristics	Total number (n= 385)
Gender	
Male	190 (49.4%)
Female	195 (50.6%)
Age (years)	70.03±12.58
BMI (kg/m^2)	25.95±4.75
Smoking	
Non-smoker	274 (71.2%)
Ex-smoker	72 (18.7%)
Smoker	39 (10.1%)
Duration of DM (years)	9.76±8.05
Hemoglobin A1c (%)	6.87±1.17
eGFR (mL/min/1.73m^2)	70.45±24.36
Blood Pressure	
Systolic BP (mmHg)	131.9±17.0
Diastolic BP (mmHg)	71.4±11.7
urine ACR level (mg/mmol)	35.9±84.0
Co-morbidities:	
HT	360 (93.5%)
CVD (IHD or CVA or PVD)	
IHD	20(5.2%)
CVA	43 (11.2%)
PVD	1 (0.3%)
Lipid Profile	
TG (mmol/L)	1.52±1.1
TC (mmol/L)	4.28±0.91
HDL (mmol/L)	1.32±0.38
LDL (mmol/L)	2.27±0.75

Current use of ACEI/ARB	
ACEI	
ARB	194 (50.4%)
	62 (16.1%)

Table 2. Demographic profiles of physicians who have attended the recruited DM cases with proteinuria

Physicians characteristics	Total number (n= 58)
Gender	
Male	35
Female	23
Duration of clinical practice (years)	15.4±9.2
Duration of clinical practice (years)	
≤ 5	7
6-10	14
11-20	22
≥ 21	15
FM training status	
None	13
Basic FM training/DFM	13
Intermediate fellow	16
HKAM FM specialist	16

Data are shown as mean ± standard deviation or number (n) of cases

Table 2.1 Sub-analysis of attending doctors' profile according to duration of clinical practice and FM training status.

Duration of clinical practice	FM training status					P value
	None	Basic FM training/DFM	Intermediate fellow	HKAM FM specialist	Total	
≤5 years	0	6	1	0	7	**0.000**
6-10 years	0	5	8	1	14	
11-20 years	1	2	6	13	22	
≥21 years	12	0	1	2	15	
Total	13	13	16	16	58	

Table 3. Comparisons of the prevalence of TI according to attending doctors' profile

Doctor's profile	Total cases (n=385)	With TI (n=155)	Without TI (n=230)	Prevalence of TI (40.3%)	P value
Gender					
Male	232	105	127	45.3%	0.014
Female	153	50	103	32.7%	
Duration of clinical practice					
Average (years)	13.3±8.4	15.6±9.4	11.8±7.3		0.000
≤5 years	52	17	35	32.7%	0.000
6-10 years	91	26	65	28.6%	
11-20 years	162	65	97	40.1%	
≥21 years	80	47	33	58.8%	
Training status					
Non	78	42	36	53.8%	0.006
With FM training	307	113	194	36.8%	0.525
Basic	117	41	76	35.0%	
Intermediate fellow	96	33	63	34.4%	
FM specialist	94	39	55	41.5%	

Data are shown as mean ± standard deviation or No. (%) of cases

Abbreviations:

Table 4. Study on patients' profile in the presence or absence of therapeutic inertia (TI) *

Patients characteristics	Without TI (n=230)	With TI (n=155)	P-value
Sex	116	74	0.604
	114	81	
Age (years)	69.6±11.8	70.6±13.7	0.471
BMI (kg/m^2)	25.37±4.85	25.33±4.53	0.603
Smoking	168	106	0.543
	39	33	
Smoker	23	16	
Duration of DM (years)	9.46±7.5	10.2±8.8	0.366
Haemoglobin A1c (%)	6.88±1.22	6.85±1.11	0.811
eGFR ($ml/min/1.73m^2$)	70.1±24.4	71.0±24.4	0.702
Urine ACR level (mg/mmol)	39.1±72.4	31.0±98.8	0.356
Different category of proteinuria			
2.5/3.5-30	160 (69.6%)	132 (85.2%)	**0.001**
30-300	66 (28.7%)	20 (12.9%)	
>300	4 (1.7%)	3 (1.9%)	
Blood pressure Systolic	134.6±18.6	128.0±13.6	**0.000**
(mmhg) Diastolic	72.5±12.2	69.9±10.8	**0.036**
Treatment with ACEI/ARB			
Nil	64 (28.8%)	64 (41.3%)	**0.000**
On submaximal dose of ACEI/ARB	46 (20.0%)	88 (56.8%)	
On maximum dose of ACEI/ARB	120 (52.2%)	3 (1.9%)	
HT	220 (95.7%)	140 (90.3%)	**0.037**
CVD			
IHD	11 (4.8%)	9 (5.8%)	0.657
CVA	30 (13.1%)	15 (9.7%)	0.371
PVD	0 (0%)	1 (0.6%)	0.403
Other diabetic complications			

With diabetic retinopathy	98(42.6%)	65 (41.9%)	0.90
Diabetic neuropathy	36 (15.7%)	21 (13.5%)	0.569
Lipid Profile			
TG (mmol/L)	1.50±1.05	1.55±1.18	0.654
TC (mmol/L)	4.31±0.9	4.23±0.93	0.429
HDL (mmol/L)	1.34±0.39	1.29±0.37	0.203
LDL (mmol/L)	2.29±0.71	2.250.80	0.553

Table 5. Logistic regression analysis on associating factors contributing to the presence of therapeutic inertia on proteinuria management among T2DM patients.

Independent variables	Odds ratio	95% C.I.for EXP(B)		P value
		Lower	Upper	
Systolic blood pressure reading	0.97	0.95	0.99	**0.001**
Urine ACR being 2.5/3.5-30 mg/mmol	0.37	0.18	0.73	**0.004**
On submaximal dose of ACEI	2.40	1.30	4.44	**0.005**
Drs' year of practice (≥21 yrs)	4.29	1.64	11.19	**0.003**

Appendix

Appendix: Data collection form for TI study on proteinuria management among T2DM patients managed in the primary care

	Case 1	Case 2	Case 3...
A. Patients characteristics			
Gender (male/female)			
Age (years)			
BMI (kg/m^2)			
Smoking (Never, smoker, ex-smoker)			
Duration of DM (years)			
Latest urine ACR level			
Haemoglobin A1c (%)			
eGFR (mL/min/1.73m^2)			
Blood Pressure (mmHg) (systolic BP and diastolic BP)			
Current use of ACEI or ARB (yes or no) If yes, name and dosage of drug			
Co-morbidities:			
HT			
IHD			
CVA			
PVD			
Lipid Profile			
TG (mmol/L)			
TC (mmol/L)			
HDL (mmol/L)			
LDL (mmol/L)			
B. Physician Characteristics			
Gender (Male/female)			
Duration of clinical practice (years)			
FM training status: 1. None 2. Basic/DFM			

3. Intermediate fellow 4. FM specialist
C. Escalation of proteinuria treatment (yes or no)
If yes: ACEI/ARB initiated or dosage augmented
If no: justification for not escalating treatment (yes or no) If yes: details of justification* If no: defined as true TI

***Details of justification for not escalating treatment:**

1. ACEI/ARB is contraindicated due to drug allergy, with history of renal artery stenosis, or patients' blood pressure on attendance has been low (<90/60mmhg);
2. Patients' intolerance to the side effects of ACEI/ARB: such as with prior history of drug induced renal impairment or hyperkalemia (serum K>5.0mmol/L) etc.
3. Other causes of increased ACR needs to be excluded, e.g. urinary tract infection etc.
4. Patients' non-compliance to the existing ACEI/ARB regime and advice on regular drug compliance was given;
5. Patients' refusal to start ACEI/ARB.
6. Patients are taking the maximum dosage of ACEI/ARB

Figures

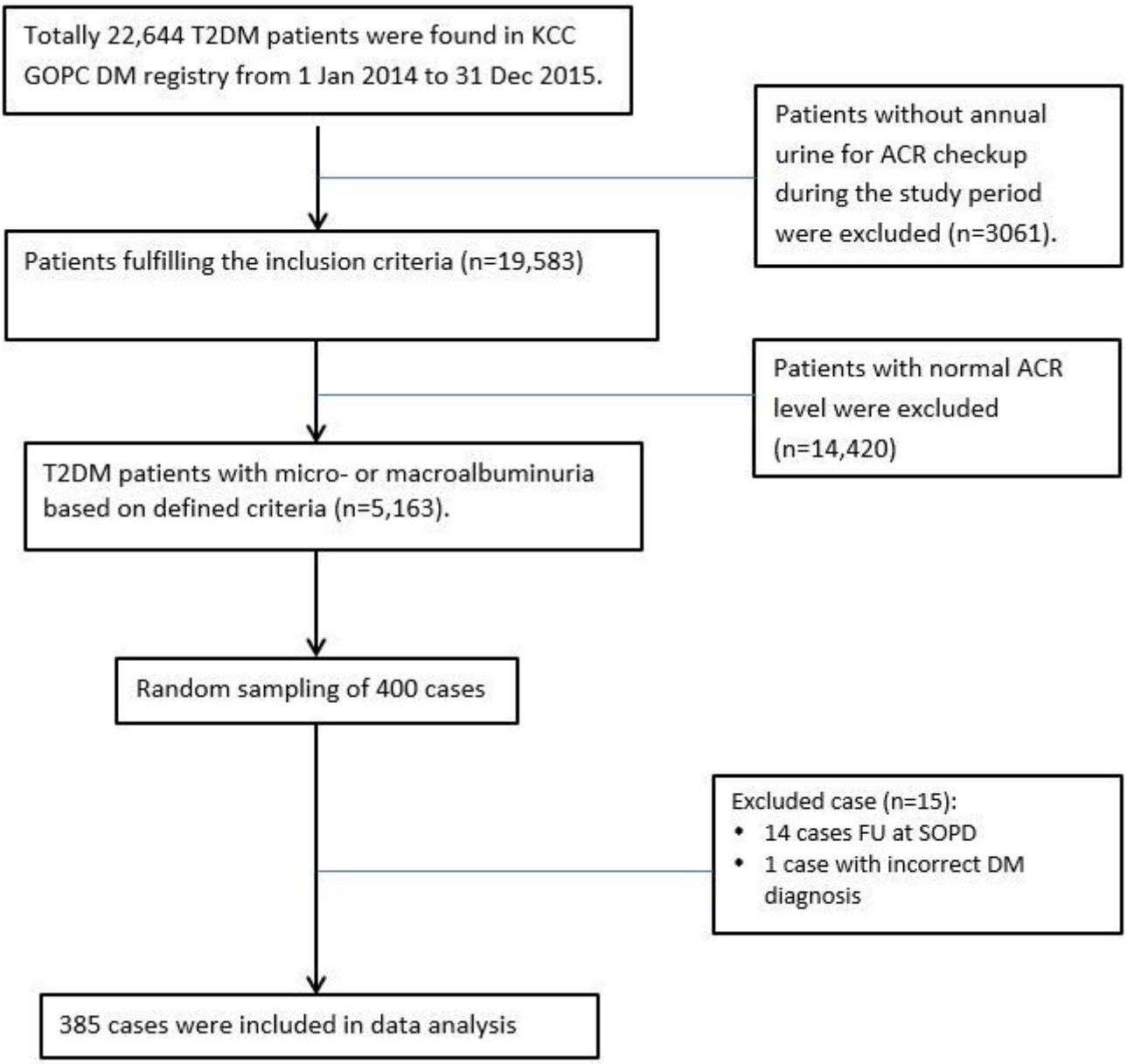
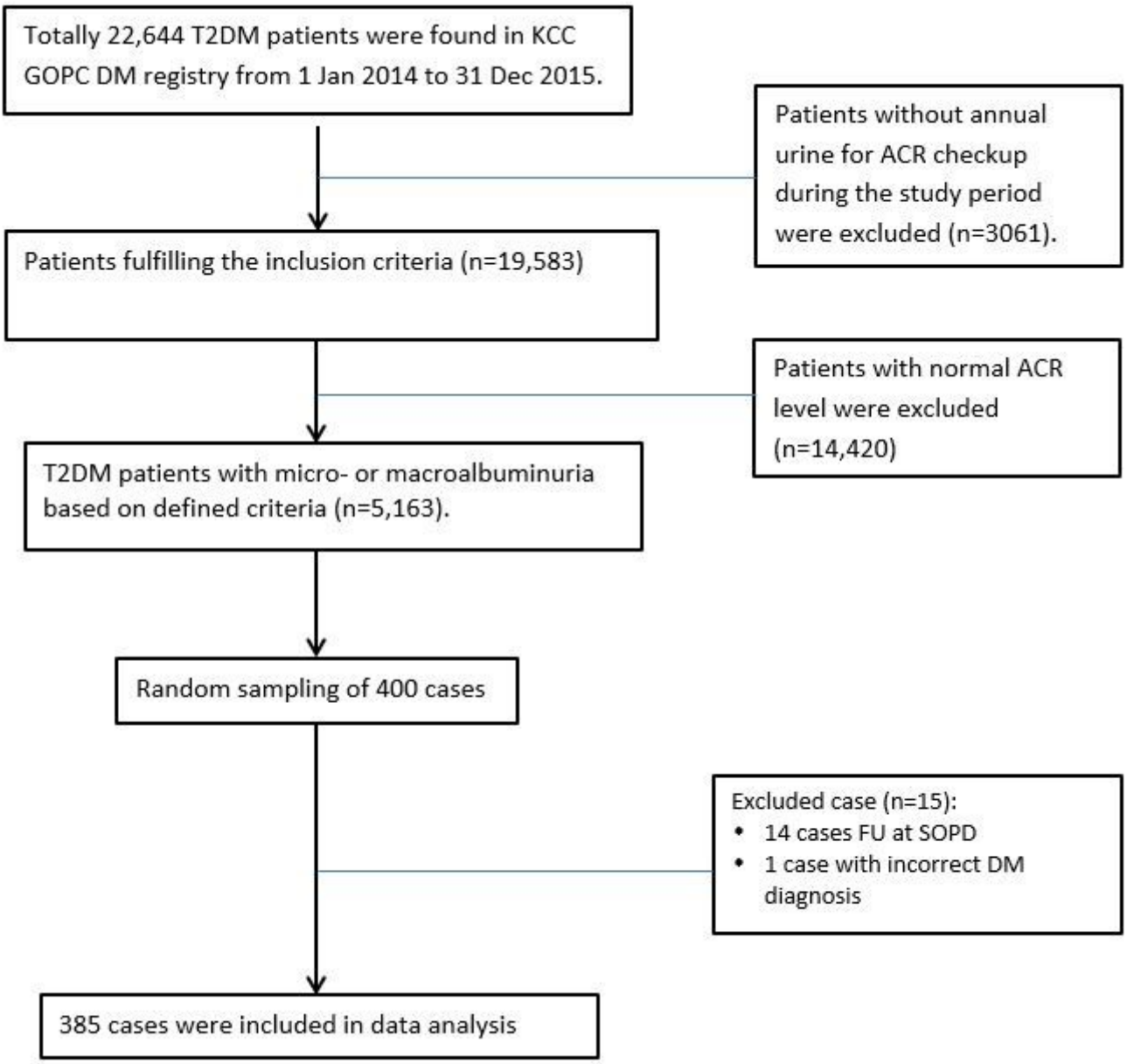


Figure 1

Flow chart of sampling approach and patient recruitment of this study.



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